

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: C07D 471/04, A61K 31/519, A61P 9/00, A61P 25/00, C07D 221/00, C07D 239/00, C07D 451/00, C07D 471/00, C07D 519/00	A1	(11) International Publication Number: WO 00/23444 (43) International Publication Date: 27 April 2000 (27.04.2000)
--	----	---

(21) International Application Number: PCT/US99/24901	Published
(22) International Filing Date: 21 October 1999 (21.10.1999)	
(30) Priority Data: 09/176,521 21 October 1998 (21.10.1998) US	
(60) Parent Application or Grant ABBOTT LABORATORIES [/]; () BHAGWAT, Shripad, S. [/]; () LEE, Chih-Hung [/]; () COWART, Marlon, D. [/]; () McKIE, Jeffrey, A. [/]; () GRILLOT, Anne, Laure [/]; () STEWART, Andrew, O. [/]; () ZHENG, Guo, Zhu [/]; () PERNER, Richard, J. [/]; () MILLER, Robert, A. : ()	

(54) Title: **5,7-DISUBSTITUTED-4-AMINOPYRIDO[2,3-D]PYRIMIDINE COMPOUNDS**
 (54) Titre: **COMPOSES DE 4-AMINOPYRIDO[2,3-D]PYRIMIDINE A DISUBSTITUTION 5,7**

(57) Abstract

A method of inhibiting adenosine kinase by administering one of more compounds of formula (I), wherein R₁, R₂, R₃ and R₄ are defined, a pharmaceutical composition comprising a therapeutically effective amount of a compound thereof above in combination with a pharmaceutically acceptable carrier, and a method of treating cerebral ischemia, epilepsy, nociception, inflammation and sepsis in a mammal in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound thereof, a process for preparing said compounds, and compounds having the above formula wherein R₁, R₂, R₃ and R₄ are separately defined.

(57) Abrégé

Cette invention a trait à une technique d'inhibition de l'adénosine kinase par administration d'un ou de plusieurs composés correspondant à la formule (I), formule dans laquelle, R₁, R₂, R₃ et R₄ sont définis. Elle concerne également une composition pharmaceutique renfermant une quantité efficace du point de vue thérapeutique du composé susmentionné associé à un excipient acceptable du point de vue pharmaceutique. Elle porte, de surcroît, sur une méthode de traitement de l'ischémie cérébrale, de l'épilepsie, de la perception nociceptive, de l'inflammation et de la septicémie, laquelle méthode consiste à administrer au sujet mammalien une quantité efficace du point de vue thérapeutique de ce composé. Elle concerne, en outre, un procédé de préparation desdits composés et des composés correspondant à la formule (I), formule dans laquelle R₁, R₂, R₃ et R₄ sont définis séparément.

PCT

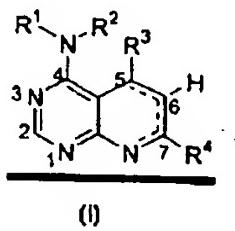
WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 471/04, A61K 31/519, A61P 25/00, 9/00, C07D 519/00 // (C07D 471/04, 239/00, 221/00) (C07D 519/00, 471/00, 451/00) (C07D 519/00, 471/00, 471/00)		A1	(11) International Publication Number: WO 00/23444 (43) International Publication Date: 27 April 2000 (27.04.00)
(21) International Application Number: PCT/US99/24901 (22) International Filing Date: 21 October 1999 (21.10.99)		(74) Agents: MILLER, Robert, A. et al.; Abbott Laboratories, CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).	
(30) Priority Data: 09/176,521 21 October 1998 (21.10.98) US		(81) Designated States: CA, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(71) Applicant: ABBOTT LABORATORIES (US/US); CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(72) Inventors: BHAGWAT, Shripad, S.; 5015 Ashley Falls Court, San Diego, CA 92130 (US). LEE, Chih-Hung; 966 Dunhill Road, Grayslake, IL 60030 (US). COWART, Marlon, D.; 43 E. Dahlia Lane, Round Lake Beach, IL 60073 (US). MCKIE, Jeffrey, A.; 5555 Oberlin Drive, San Diego, CA 92121 (US). GRIJALLOT, Anne, Laure; Apartment #2, 99 Hammond Street, Cambridge, MA 02138 (US). STEWART, Andrew, O.; 1289 Thombury Lane, Libertyville, IL 60048 (US). ZHENG, Guo, Zhu; 29609 N. Birch, Lake Bluff, IL 60044 (US). PERNER, Richard, J.; 704 Penny Lane, Gurnee, IL 60031 (US).			

(54) Title: 5,7-DISUBSTITUTED-4-AMINOPYRIDO[2,3-D]PYRIMIDINE COMPOUNDS



(57) Abstract

A method of inhibiting adenosine kinase by administering one or more compounds of formula (I), wherein R¹, R², R³ and R⁴ are defined, a pharmaceutical composition comprising a therapeutically effective amount of a compound thereof above in combination with a pharmaceutically acceptable carrier, and a method of treating cerebral ischemia, epilepsy, nociception, inflammation and sepsis in a mammal in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound thereof, a process for preparing said compounds, and compounds having the above formula wherein R¹, R², R³ and R⁴ are separately defined.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Bahamas	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		

Description

5

10

15

20

25

30

35

40

45

50

55

5

5.7-DISUBSTITUTED-4-AMINOPYRIDO[2,3-D]PYRIMIDINE COMPOUNDS

10

This application is a continuation in part of copending U.S. Patent Application Serial No. 09/176,521 filed October 21, 1998 which in turn is a continuation in part of copending U.S. Patent Application Serial No. 09/062,796 filed April 13, 1998, which in turn is a conversion of Provisional U.S. Patent Application Serial No. 60/043,251, filed

15

5 April 16, 1997.

TECHNICAL FIELD

20

The present invention relates to a method of inhibiting adenosine kinase by administering 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidine compounds to a mammal in need of such treatment, to pharmaceutical compositions containing such compounds, as well as to certain 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidine compounds.

25

BACKGROUND OF THE INVENTION

30

Adenosine kinase (ATP:adenosine 5'-phosphotransferase, EC 2.7.1.20) is a ubiquitous enzyme which catalyzes the phosphorylation of adenosine to adenosine monophosphate (AMP), using adenosine triphosphate (ATP), preferentially, as the phosphate source. Magnesium is also required for the reaction, and the true cosubstrate is probably the MgATP²⁻ complex (Palella, et al., *J. Biol. Chem.* 1980, 255: 5264-5269).

35

Adenosine kinase has been isolated from yeast (Leibach, et al., *Hoppe-Seyler's Z. Physiol. Chem.* 1971, 352: 328-344), a variety of mammalian sources (e.g. Miller, et al., *J. Biol. Chem.* 1979, 254: 2339-2345; Palella, et al., *J. Biol. Chem.* 1980, 255: 5264-5269; Yamada, et al., *Comp. Biochem. Physiol.* 1982, 71B: 367-372; Rottlan and Miras-Portugal, *Eur. J. Biochem.*, 1985, 151: 365-371), and certain microorganisms (e.g. Lobelle-Rich and Reeves, *Am. J. Trop. Med. Hyg.* 1983, 32: 976-979; Datta, et al., *J. Biol. Chem.* 1987, 262: 5515-5521). It has been found to be present in virtually every human tissue assayed including kidney, liver, brain, spleen, placenta and pancreas (Andres and Fox, *J. Biol. Chem.* 1979, 254: 11388-11393).

50

-1-

55

5

10

15

20

25

30

35

40

45

50

Adenosine kinase is a key enzyme in the control of intracellular adenosine concentration (Arch and Newsholme, Essays Biochem. 1978, 14: 82-123). Adenosine is a purine nucleoside that is an intermediate in the purine nucleotide degradation and salvage. Adenosine also has many important physiologic effects, many of which are mediated

- 5 through the activation of specific ectocellular receptors, termed P1 receptors (Burnstock, in Cell Membrane Receptors for Drugs and Hormones, 1978, (Bolis and Straub, eds.) Raven, New York, pp. 107-118; Fredholm, et al., Pharmacol. Rev. 1994, 46: 143-156).

In the central nervous system, adenosine inhibits the release of certain neurotransmitters (Corradetti, et al., Eur. J. Pharmacol. 1984, 104: 19-26), stabilizes membrane potential (Rudolphi, et al., Cerebrovasc. Brain Metab. Rev. 1992, 4: 346-360), functions as an endogenous anticonvulsant (Dragunow, Trends Pharmacol. Sci. 1986, 7: 128-130) and may have a role as an endogenous neuroprotective agent (Rudolphi, et al., Trends Pharmacol. Sci., 1992, 13: 439-445). Adenosine may play a role in several disorders of the central nervous system such as schizophrenia, anxiety, depression and

- 15 Parkinson's disease (Williams, M., in Psychopharmacology: The Fourth Generation of Progress, Bloom, Kupfer (eds.), Raven Press, New York, 1995, pp 643-655. Adenosine has also been implicated in modulating transmission in pain pathways in the spinal cord (Sawynok, et al., Br. J. Pharmacol., 1986, 88: 923-930), and in mediating the analgesic effects of morphine (Sweeney, et al., J. Pharmacol. Exp. Ther. 1987, 243: 657-665).

20 Adenosine also, inhibits certain neutrophil functions and exhibits anti-inflammatory effects (Cronstein, J. Appl. Physiol. 1994, 76: 5-13). An AK inhibitor has been reported to decrease paw swelling in a model of adjuvant arthritis in rats (Firestein, et.al., Arthritis and Rheumatism, 1993, 36, S48.

25 Adenosine also exerts a variety of effects on the cardiovascular system, including vasodilation, impairment of atrioventricular conduction and endogenous cardioprotection in myocardial ischemia and reperfusion (Mullane and Williams, in Adenosine and Adenosine Receptors, 1990 (Williams, ed.) Humana Press, New Jersey, pp. 289-334). The widespread actions of adenosine also include effects on the renal, respiratory, gastrointestinal and reproductive systems, as well as on blood cells and adipocytes.

55

5

Adenosine, via its Λ_1 receptor activation on adipocytes, plays a role in diabetes by inhibiting lipolysis (Londos, et al., *Proc. Natl. Acad. Sci. USA*, 1980, 77, 2551).

10

Endogenous adenosine release appears to have a role as a natural defense mechanism in various pathophysiologic conditions, including cerebral and myocardial

15

ischemia, seizures, pain, inflammation and sepsis. While adenosine is normally present at low levels in the extracellular space, its release is locally enhanced at the site(s) of excessive cellular activity, trauma or metabolic stress. Once in the extracellular space, adenosine activates specific extracellular receptors to elicit a variety of responses which tend to restore cellular function towards normal (Bruns, *Nucleosides Nucleotides*, 1991,

20

10: 931-943; Miller and Hsu, *J. Neurotrauma*, 1992, 9: S563-S577). Adenosine has a half-life measured in seconds in extracellular fluids (Moser, et al., *Am. J. Physiol.* 1989, 25: C799-C806), and its endogenous actions are therefore highly localized.

25

The inhibition of adenosine kinase can result in augmentation of the local adenosine concentrations at foci of tissue injury, further enhancing cytoprotection. This effect is likely to be most pronounced at tissue sites where trauma results in increased adenosine production, thereby minimizing systemic toxicities.

30

Pharmacologic compounds directed towards adenosine kinase inhibition provide potentially effective new therapies for disorders benefited by the site- and event-specific potentiation of adenosine. Disorders where such compounds may be useful include

35

20 ischemic conditions such as cerebral ischemia, myocardial ischemia, angina, coronary artery bypass graft surgery (CABG), percutaneous transluminal angioplasty (PTCA), stroke, other thrombotic and embolic conditions, and neurological disorders such as epilepsy, anxiety, schizophrenia, nociception including pain perception, neuropathic pain, visceral pain, as well as inflammation, arthritis, immunosuppression, sepsis, diabetes

40

25 and gastrointestinal dysfunctions such as abnormal gastrointestinal motility.

45

A number of compounds have been reported to inhibit adenosine kinase. The most potent of these include 5'-amino-5'-deoxyadenosine (Miller, et al., *J. Biol. Chem.* 1979, 254: 2339-2345), 5-iodotubercidin (Wotring and Townsend, *Cancer Res.* 1979, 39: 3018-3023) and 5'-deoxy-5-iodotubercidin (Davies, et al., *Biochem. Pharmacol.* 1984, 33: 347-355).

50

5

10

15

20

25

30

35

40

45

50

55

Adenosine kinase is also responsible for the activation of many pharmacologically active nucleosides (Miller, et al., J. Biol. Chem., 1979, 254: 2339-2345), including tubercidin, formycin, ribavirin, pyrazofurin and 6-(methylmercapto)purine riboside. These purine nucleoside analogs represent an important group of antimetabolites which possess cytotoxic, anticancer and antiviral properties. They serve as substrates for adenosine kinase and are phosphorylated by the enzyme to generate the active form. The loss of adenosine kinase activity has been implicated as a mechanism of cellular resistance to the pharmacological effects of these nucleoside analogs (e.g. Bennett, et al., Mol. Pharmacol., 1966, 2: 432-443; Caldwell, et al., Can. J. Biochem., 1967, 45: 735-744; Suttle, et al., Europ. J. Cancer, 1981, 17: 43-51). Decreased cellular levels of adenosine kinase have also been associated with resistance to the toxic effects of 2'-deoxyadenosine (Hershfield and Kredich, Proc. Natl. Acad. Sci. USA, 1980, 77: 4292-4296). The accumulation of deoxyadenosine triphosphate (dATP), derived from the phosphorylation of 2'-deoxyadenosine, has been suggested as a toxic mechanism in the immune defect associated with inheritable adenosine deaminase deficiency (Kredich and Hershfield, in The Metabolic Basis of Inherited Diseases, 1989 (Scriver, et al., eds.), McGraw-Hill, New York, pp. 1045-1075).

B.S. Hurlbert et al. (J. Med. Chem., 11: 711-717 (1968)) disclose various 2,4-diaminopyrido[2,3-d]pyrimidine compounds having use as antibacterial agents. R. K. Robins et al. (J. Amer. Chem. Soc., 80:3449-3457 (1958)) disclose methods for preparing a number of 2,4-dihydroxy-, 2,4-diamino-, 2-amino-4-hydroxy- and 2-mercaptop-4-hydroxypyrido[2,3-d]pyrimidines having antifolic acid activity. R. Sharma et al., (Indian J. Chem., 31B: 719-720 (1992)) disclose 4-amino-5-(4-chlorophenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine and 4-amino-5-(4-methoxyphenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine compounds having antibacterial activity. A. Gupta et al., (J. Indian Chem. Soc., 71: 635-636 (1994)) disclose 4-amino-5-(4-fluorophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine and 4-amino-5-(4-chlorophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine compounds having antibacterial activity. L. Prakash et al., (Pharmazie, 48: 221-222 (1993)) disclose 4-amino-5-phenyl-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine, 4-amino-5-phenyl-7-(4-bromophenyl)pyrido[2,3-

5

10

15

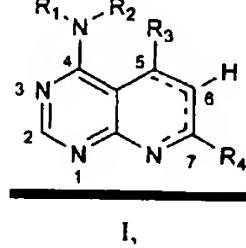
d]pyrimidine, 4-amino-5-(4-methoxyphenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine, and 4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine compounds having antifungal activity. P. Victory et al., Tetrahedron, 51: 10253-10258 (1995)) discloses the synthesis of 4-amino-5,7-diphenylpyrido[2,3-d]pyrimidine compounds from acyclic precursors. Bridges et al.(PCT application WO 95/19774, published July 27, 1995) disclose various bicyclic heteroaromatic compounds as having utility for inhibiting tyrosine kinase of epidermal growth factors.

SUMMARY OF THE INVENTION

20

The present invention provides for 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidine compounds having utility as adenosine kinase inhibitors.

In one aspect, the present invention provides a method of inhibiting adenosine kinase by administering a compound of formula I



30

15

or a pharmaceutically acceptable salt or amide thereof in vitro or to a mammal wherein, R¹ and R² are each independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxy carbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl, heterocycle, heterocyclealkyl, heterocyclecarbonyl, hydroxylalkyl, iminoalkyl, and (NZ₁Z₂)alkyl, or R¹ and R² may join together with the nitrogen atom to which they are attached to form a 5-7 membered ring optionally containing 1-2 additional heteroatoms selected from the group consisting of O, N, and S;

45

Z₁ and Z₂ are each independently selected from the group consisting of hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, benzyl, benzyloxycarbonyl, and formyl;

50

55

5

R^3 is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocycloalkylcarbonyl, $(N\bar{Z}_1\bar{Z}_2)alkyl$, and $-R^A R^B$;

10

R^A is selected from the group consisting of aryl and arylalkyl;

5 R^B is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

15

R^4 is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and $-R^C R^D R^E$;

10 R^C is selected from the group consisting of aryl, arylalkyl, heterocycle, and heterocyclealkyl;

20

R^D is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl;

25

15 R^E is absent or selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and,

30

20 a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;

35

with the proviso that the following compounds are excluded,

4-amino-5-(4-chlorophenyl)-7-(4-nitrophenyl)pyridol[2,3-d]pyrimidine,

4-amino-5-(4-methoxyphenyl)-7-(4-nitrophenyl)pyridol[2,3-d]pyrimidine,

4-amino-5-(4-fluorophenyl)-7-(4-fluorophenyl)pyridol[2,3-d]pyrimidine,

40

25 4-amino-5-(4-chlorophenyl)-7-(4-fluorophenyl)pyridol[2,3-d]pyrimidine,

4-amino-5-phenyl-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-phenyl-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(4-methoxyphenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine, and

30 4-amino-5,7-diphenylpyrido[2,3-d]pyrimidine.

50

5

10

In particular, the method of inhibiting adenosine kinase comprises exposing an adenosine kinase to an effective inhibiting amount of a compound of Formula I of the present invention. Where the adenosine kinase is located in vivo, the compound is administered to the organism.

15

5 In still another aspect, the present invention provides a method of treating ischemia, neurological disorders, nociception, inflammation, immunosuppression, gastrointestinal dysfunctions, diabetes and sepsis in a mammal in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound of Formula I of the present invention.

20

25

10 In a preferred aspect, the present invention provides a method of treating cerebral ischemia, myocardial ischemia, angina, coronary artery bypass graft surgery, percutaneous transluminal angioplasty, stroke, thrombotic and embolic conditions, epilepsy, anxiety, schizophrenia, pain perception, neuropathic pain, visceral pain, arthritis, sepsis, diabetes and abnormal gastrointestinal motility in a mammal in need of such treatment, comprising 15 administering to the mammal a therapeutically effective amount of a compound of Formula I of the present invention.

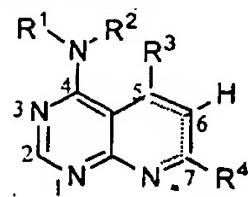
30

The present invention also contemplates the use of pharmaceutically acceptable salts and amides of compounds having Formula I.

In another aspect, the present invention provides a compound of formula I

35

20



I,

40

or a pharmaceutically acceptable salt or amide thereof wherein

45

R¹ and R² are each independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, 25 alkylcarbonyl, aminocarbonyl, aryl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl, heterocycle, heterocycloalkyl, heterocyclecarbonyl, hydroxyalkyl, iminoalkyl, and (NZ₁Z₂)alkyl, or R¹ and R² may join

50

5

together with the nitrogen atom to which they are attached to form a 5-7 membered ring optionally containing 1-2 additional heteroatoms selected from the group consisting of O, N, and S:

10

Z_1 and Z_2 are each independently selected from the group consisting of hydrogen,

5 alkoxy carbonyl, alkyl, alkyl carbonyl, benzyl, benzyloxycarbonyl, and formyl;
 R^3 is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, $(NZ_1Z_2)alkyl$, and $-R^A R^B$;

15

R^A is selected from the group consisting of aryl and arylalkyl;

20

10 R^B is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

25

R^4 is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and $-R^C R^D R^E$;

30

15 R^C is selected from the group consisting of aryl, arylalkyl, heterocycle, and heterocyclealkyl;

R^D is selected from the group consisting of aryl, arylalkoxy, arylalkoxymino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl;

35

20 R^E is absent or is selected from the group consisting of aryl, arylalkoxy, arylalkoxymino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

40

25 a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;

45

with the proviso that the compound may not be selected from the group consisting of:

4-amino-5-(4-chlorophenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-methoxyphenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine;

30 4-amino-5-(4-fluorophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine;

50

5

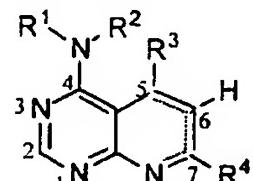
- 4-amino-5-(4-chlorophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine;
 4-amino-5-phenyl-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine;
 4-amino-5-phenyl-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;
 4-amino-5-(4-methoxyphenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine;
 4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine; and
 4-amino-5,7-diphenylpyrido[2,3-d]pyrimidine.

15

In another aspect, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I above in combination with a pharmaceutically acceptable carrier.

20

In another aspect, the present invention provides a process for the preparation of adenosine kinase inhibiting compounds of formula I



I,

25

wherein

15 R¹ and R² are hydrogen;

R³ is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, (NZ₂)alkyl, and -R^AR^B;

R^A is selected from the group consisting aryl and arylalkyl;

20 R^B is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

40 R⁴ is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and -R^CR^DR^E;

R^C is selected from the group consisting of aryl, arylalkyl, heterocycle, and

45 heterocyclealkyl;

R^D is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl,

50

5

heterocycleimino, heterocycleoxy, heterocycloxyalkyl, heterocycloxyimino, heterocycloxyiminoalkyl, and heterocyclesulfonyl; and

10

R^E is absent or is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocylealkoxy, heterocyclealkyl,

5 heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycloxyalkyl, heterocycloxyimino, heterocycloxyiminoalkyl, and heterocyclesulfonyl; and

15

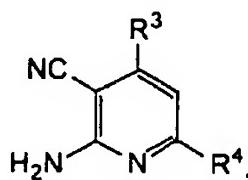
a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;

the method comprising

20

(a) reacting a ketone having the formula $R^4\text{-CO-CH}_3$, wherein R^4 is as defined above, with an aldehyde having the formula $R^3\text{-CHO}$, wherein R^3 is as defined above and malononitrile in the presence of an ammonium salt under anhydrous conditions and isolating a first intermediate compound having the structure

25



30

15 (b) reacting the first intermediate compound with formamide at reflux for from about 1 to about 8 hours, and isolating the compound of formula I which has a double bond between the 5,6 carbons and a double bond between the 7 carbon and the 8 nitrogen, and then,

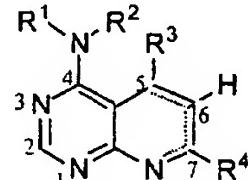
35

(c) optionally reducing the compound from step (b) to form a partially reduced or fully reduced right side of formula I by catalytic hydrogenation.

40

20 In another aspect, the present invention provides a process for the preparation of adenosine kinase inhibiting compounds of formula I

45



I,

wherein

50

5

R¹ and R² are hydrogen;

10

R³ is selected from the group consisting of alkynyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, (NZ₁Z₂)alkyl, and -R^AR^B;

15

R^A is selected from the group consisting of aryl and arylalkyl;

20

R^B is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

25

R⁴ is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and -R^CR^DR^E;

30

R^C is selected from the group consisting of aryl, arylalkyl, heterocycle, and heterocyclealkyl;

35

R^D is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino,

40

heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

45

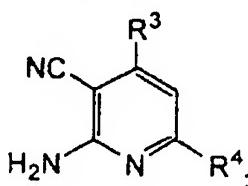
R^E is absent or is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

50

a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;

the method comprising

(a) reacting a ketone having the formula R⁴C(O)CH₃, wherein R⁴ is as defined above, with an dicyanoalkene compound having the formula R³CH=C(CN)₂, wherein R³ is as defined above by heating at reflux and isolating a first intermediate compound having the structure



55

5

10

15

20

25

30

35

40

50

- (b) reacting the first intermediate compound with formamide at reflux for from about 1 to about 8 hours, and isolating the compound of formula I which has a double bond between the 5 and 6 carbons and a double bond between the 7 carbon and the 8 nitrogen and
- 5 (c) optionally reducing the compound from step (b) to form a partially reduced or fully reduced right side of formula I by catalytic hydrogenation.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidine compounds that are useful in inhibiting adenosine kinase, to pharmaceutical compositions containing such compounds, to a method of using such compounds for inhibiting adenosine kinase, to novel 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidine compounds and to a process of preparing 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidine compounds.

15 In one aspect, the present invention provides 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidine compounds that are adenosine kinase inhibitors. An adenosine kinase inhibitor of the present invention is a compound of the Formula I, shown above.

As summarized above, the present invention relates to a method of inhibiting adenosine kinase comprising administering a compound of formula I



wherein

R¹ and R² are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, 25 aminocarbonyl, aryl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl, heterocyclealkyl, hydroxyalkyl, iminoalkyl, and (NZ₁Z₂)alkyl, or R¹ and R² may join together with the nitrogen atom to which they are attached to form a 6 membered ring

55

5

optionally containing 1 additional heteroatom selected from the group consisting of O, N, and S;

10

R^3 is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heterocycloalkyl, $(N_1Z_2)alkyl$, and $-R^A R^B$;

5 R^A is selected from the group consisting of aryl and arylalkyl;

15

R^B is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, and heterocycle;

20

R^4 is selected from the group consisting of alkoxyalkynyl, alkynyl, aryl, heterocycle, and $-R^C R^D R^E$;

10 R^C is selected from the group consisting of aryl and heterocycle;

25

R^D is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, heterocycloalkoxy, heterocycloalkyl, heterocyclecarbonyl, heterocycleoxy, and heterocyclesulfonyl;

30

R^E is absent or selected from the group consisting of aryl, arylalkoxy,

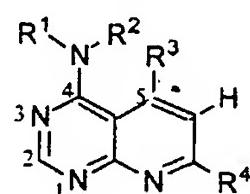
15 arylalkoxymino, arylalkyl, aryloxy, heterocycle, heterocycloalkoxy, heterocycloalkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, and heterocycleoxyiminoalkyl; and

35

a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained.

20 The preferred compounds utilized in the above method of inhibiting adenosine kinase are selected from a compound of formula II

40



II.

wherein

45

R^1 and R^2 are each independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxy carbonyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl,

50

5

heterocyclealkyl, hydroxyalkyl, iminoalkyl, and (NZ₁Z₂)alkyl, or R¹ and R² may join together with the nitrogen atom to which they are attached to form a 6 membered ring optionally containing 1 additional heteroatom selected from the group consisting of O, N, and S;

10

5 R³ is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heterocyclealkyl, (NZ₁Z₂)alkyl, and -R^AR^B;

15

R^A is selected from the group consisting of aryl and arylalkyl;

R^B is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, and heterocycle;

20

10 R⁴ is selected from the group consisting of alkoxyalkynyl, alkynyl, aryl, heterocycle, and -R^CR^DR^E;

R^C is selected from the group consisting of aryl and heterocycle;

25

R^D is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleoxy, and heterocyclesulfonyl; and

30

R^E is absent or is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, and heterocycleoxyiminoalkyl.

35

20 In a preferred embodiment, an adenosine kinase inhibitor of the present invention is a compound of Formula II above, wherein R⁴ is aryl or heterocycle and substituted versions thereof or -R^CR^DR^E.

40

In a more preferred embodiment, an adenosine kinase inhibitor of the present invention is a compound of Formula II above, wherein R⁴ is aryl or heterocycle and substituted versions thereof and R³ is alkyl, aryl, arylalkyl or heterocycle and substituted versions thereof wherein the substituents are as identified above.

45

In another preferred embodiment, an adenosine kinase inhibitor of the present invention is a compound of Formula I above, wherein R⁴ is selected from the group consisting of: phenyl; thiophene-2-yl; 3-methyl-2-oxobenzoxazolin-6-yl; 2-(dimethylamino)-5-pyrimidinyl; 2-(N-formyl-N-methyl amino)-5-pyrimidinyl; 2-(N-

50

5

methoxyethyl-N-methyl amino)-5-pyrimidinyl; 2-(N-methylamino)-5-pyrimidinyl; 2-(1-morpholinyl)-5-pyrimidinyl; 2-(1-pyrrolidinyl)-5-pyrimidinyl; 2-dimethylamino-5-

10

pyrimidinyl; 2-furanyl; 2-oxobenzoxazolin-6-yl; 2-pyridyl; 3-(dimethylamino)phenyl; 3-amino-4-methoxyphenyl; 3-bromo-4-(dimethylamino)phenyl; 3-methoxyphenyl; 3-

5 methyl-4-(N-acetyl-N-methylamino)phenyl; 3-methyl-4-(N-formyl-N-

15

methylamino)phenyl; 3-methyl-4-(N-methyl-N-(trifluoroacetyl)amino)phenyl; 3-methyl-4-(N-methylamino)phenyl; 3-methyl-4-pyrrolidinylphenyl; 3-pyridyl; 3,4-dichlorophenyl;

20

3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; 4-(acetylamino)phenyl; 4-(dimethylamino)-3-fluorophenyl; 4-(dimethylamino)phenyl; 4-(imidazol-1-yl)phenyl; 4-

10 (methylthio)phenyl; 4-(morpholinyl)phenyl; 4-(N-(2-(dimethylamino)ethyl)amino)phenyl;

25

4-(N-(2-methoxyethyl)amino)phenyl; 4-(N-acetyl-N-methylamino)phenyl; 4-(N-ethyl-N-

30

formylamino)phenyl; 4-(N-ethylamino)phenyl; 4-(N-formyl-N-(2-

methoxyethyl)amino)phenyl; 4-(N-isopropylamino)phenyl; 4-(N-methyl-N-(2-

35

dimethylamino)ethyl)amino)phenyl; 4-(N-methyl-N-(2-(N-

phthalimidyl)acetyl)amino)phenyl; 4-(N-methyl-N-(2-cyano)ethylamino)phenyl; 4-(N-

40

methyl-N-(2-methoxyethyl)amino)phenyl; 4-(N-methyl-N-(3-

methoxy)propionylamino)phenyl; 4-(N-methyl-N-acetylamino)phenyl; 4-(N-methyl-N-

45

formylamino)phenyl; 4-(N-methyl-N-trifluoroacetylamino)phenyl; 4-(N-

morpholinyl)phenyl; 4-(thiophene-2-yl)phenyl; 4-(ureido)phenyl; 4-(2-

20 (dimethylamino)acetylamino)phenyl; 4-(2-(2-methoxy)acetylamino)ethyl)amino)phenyl;

50

4-(2-methoxy)ethoxyphenyl; 4-(2-oxo-3-oxazolidinyl)phenyl; 4-(4-methoxy-2-

butyl)phenyl; 4-(4-methylpiperidinyl)phenyl; 4-(5-pyrimidinyl)phenyl; 4-aminophenyl; 4-bromophenyl; 4-butoxyphenyl; 4-carboxamidophenyl; 4-chlorophenyl; 4-cyanophenyl; 4-

diethylaminophenyl; 4-diethylmalonylallylphenyl); 4-dimethylaminophenyl; 4-

ethoxyphenyl; 4-ethylphenyl; 4-fluorophenyl; 4-hydroxyphenyl; 4-imidazolylphenyl; 4-

iodophenyl; 4-isopropylphenyl; 4-methoxyphenyl; 4-methylaminophenyl; 4-

methylsulfonylphenyl; 4-morpholinylphenyl; 4-N-(2-(dimethylamino)ethyl)-N-

formylamino)phenyl; 4-N-(3-methoxypropionyl)-N-isopropyl-amino)phenyl; 4-N-ethyl-

N-(2-methoxyethyl)amino)phenyl; 4-N-formylpiperazinylphenyl; 4-nitrophenyl; 4-

30 piperidinylphenyl; 4-(3-pyridyl)phenyl; 4-pyrrolidinylphenyl; 4-t-butylacrylphenyl; 5-

55

- 5 (dimethylamino)thiophene-2-yl; 5-amino-2-pyridyl; 5-dimethylamino-2-pyrazinyl; 3-
10 dimethylaminopyridazin-6-yl; 5-dimethylamino-2-pyridyl; 5-pyrimidinylphenyl; 6-(N-methyl-N-formylamino)-3-pyridinyl; 6-(N-methyl-N-methoxyethylamino)-3-pyridinyl; 6-(2-oxo-3-oxazolidinyl)-3-pyridinyl; 6-dimethylamino-3-pyridinyl; 6-imidazolyl-3-
15 pyridinyl; 6-morpholinyl-3-pyridinyl; 6-pyrrolidinyl-3-pyridinyl; 6-(2-propyl)-3-pyridinyl; (4-formylamino)phenyl; 6-(4-oxopiperidinyl)-3-pyridazinyl; 6-(4-morpholinyliminopiperidinyl)-3-pyridazinyl; 6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridazinyl; 6-(4-methoxyiminopiperidinyl)-3-pyridazinyl; 6-phenylmethoxy-3-pyridazinyl; 6-(1,1-dioxidothiazolidin-3-yl)-3-pyridyl; 6-(1,3-dioxa-8-
20 azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1-oxa-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1,1-dioxidothiomorpholinyl)-3-pyridazinyl; 6-(1-oxa-4,4-dioxido-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1-oxa-4-oxo-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl; 6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-8-
25 yl)-3-pyridyl; 6-(N-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridylsulfonamide; 2-(1,1-dioxidothiomorpholinyl)-5-thiazoyl; 5-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-2-pyrazinyl; 2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-5-thiazoyl; 6-(hexahydro-1H-furo[3,4-c]pyrrol-5-
30 yl)-3-pyridazinyl; 6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridyl; 6-(4-methoxypiperidinyl)-3-pyridyl; 6-(4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-
35 isoindolyl)-3-pyridazinyl; 6-(4-(4-tetrahydropyranloxy)iminopiperidinyl)-3-pyridazinyl; 6-isopropoxy-3-pyridazinyl; 6-(2,4-dioxo-(1H,3H)-quinazolin-3-yl)-3-pyridyl; 6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridazinyl; 6-(4-tetrahydropyranloxy)-3-pyridazinyl; 6-morpholinylethoxy-3-pyridazinyl; 6-(4-ethoxypiperidinyl)-3-pyridazinyl; 6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(4-(2-ethoxyethoxy)piperidinyl)-3-
40 pyridazinyl; 6-((3aR,6aS)-2-oxo-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-3-pyridyl; 6-(4-(4-tetrahydropyranloxyethyl)piperidinyl)-3-pyridazinyl; 6-(3-(R)-tetrahydrofuranyloxy)piperidinyl)-3-pyridazinyl; 6-(3-(S)-tetrahydrofuranyloxy)piperidinyl)-3-pyridazinyl; 6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl; 6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-
45 pyridazinyl; 6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl; 6-(trans-3,4-bis-
50

5

ethoxy)pyrrolidinyl)-3-pyridazinyl; 6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl; 6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl; 6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl; 6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl; 6-(cis-3-amino-4-

10

hydroxy)pyrrolidinyl)-3-pyridazinyl; 6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridyl; 6-(1,5-dioxa-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(4-tertbutyl)piperidinyl-3-

15

pyridazinyl; 6-(4-N-formyl)piperidinyl-3-pyridazinyl; 6-morpholinyl-3-pyridazinyl; 4-N-1,4-dioxa-8-azaspiro[4.5]decan-8-ylbenzenesulfonamide; 4-(4-dioxa-8-

20

azaspiro[4.5]decan-8-ylcarboxamide)phenyl; 6-(3-methoxy-1,5-dioxa-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(1,5-dioxa-3-hydroxymethyl-9-

10 azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(S-O-ethyl-2-hydroxymethylpyrrolidinyl)-3-

pyridazinyl; 6-(4-acetyl-1-oxa-4,8-diazaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-((2R,3R)-

2,3-bis(methoxymethyl)-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-((2S,3S)-

2,3-dimethyl-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-(4,4-(cis-1,2-

25

dioxycyclopentane)piperidinyl)-3-pyridazinyl; 6-(4,4-(1S,2S-

15 dimethoxymethylethanedioxy)piperidinyl)-3-pyridazinyl; 6-(4,4-(cis-3,4-dioxy-

oxacyclopentane)piperidinyl)-3-pyridazinyl; 6-(4,4-(1,3-dioxy-2-

methoxypropylene)piperidinyl)-3-pyridazinyl; 6-(4,4-(1,3-dioxy-2-

30

hydroxymethylpropylene)piperidinyl)-3-pyridazinyl; 6-(4,4-(2-(2,2-spiro-

oxacyclopropane-1,3-dioxypropylene)piperidinyl)-3-pyridazinyl; 6-morpholinyl-3-

20 pyridazinyl; 6-(4-morpholinyliminopiperidinyl)-3-pyridyl; 6-(4-(N-

methylpiperazinyl)iminopiperidinyl)-3-pyridyl; 6-(4-(1,2,4-triazol-1-yl)iminopiperidinyl)-

35

3-pyridyl; 6-(4-ethylpiperidinylcarboxylate)-3-pyridyl; 2-phenylmethyl-3(2H)-

pyridazinone-6-yl; 6-(4-(morpholinylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-

morpholinylaminocarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N,N-

40

25 dimethylaminocarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-methyl-N-

methoxyethylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-

methoxyethylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-hydroxymethylpiperidinyl)-3-

45

pyridyl; 6-(4-hydroxypiperidinyl)-3-pyridyl; 6-(4-N-acetylpirerazinyl)-3-pyridyl; 6-(4-

cyanopiperidinyl)-3-pyridyl; 6-(4-N-(4-fluorophenyl)piperazinyl)-3-pyridyl; 4-

30 morpholinylbenzenesulfonamide; 4-N-4,4-ethylenedioxypiperidinylbenzenesulfonamide;

50

5

4-N-cyclopropylbenzenesulfonamide; 4-piperidinebenzenesulfonamide; 4-(4-cyanopiperidine)benzenesulfonamide; 4-N-cyclopropylmethylbenzenesulfonamide; 4-N,N-dimethylaminobenzenesulfonamide; 4-N-(S)-2-hydroxymethylpyrrolidinebenzenesulfonamide; 4-(4-hydroxypiperidine)benzenesulfonamide; 4-(*cis*-3,5-dimethylmorpholinyl)benzenesulfonamide; 3-fluoro-4-thiomorpholinylphenyl; 6-(thiomorpholinyl)-3-pyridyl; 6-(4,4-dioxothiomorpholinyl)-3-pyridyl; 4-(4,4-ethylenedioxypiperidinylcarboxamide)phenyl; 4-(N-cyclopropylcarboxamide)phenyl; 4-(morpholinylcarboxamide)phenyl; 6-N-cyclopropylamino-3-pyridyl; 4-(4-hydroxypiperidinylcarboxamide)phenyl; 6-(S)-hydroxymethylpyrrolidinyl-3-pyridazinyl; 6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridyl; 6-hexahydropyrimidine)-3-pyridyl; 6-(S)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl; 6-(R)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl; 6-(*cis*-3,4-dihydroxypyrrolidinyl)-3-pyridyl; 6-[*(3aR,6aS)*-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-2-one-5-yl]-3-pyridyl; 6-(*cis*-2,3-dihydroxypyrrolidinyl)-3-pyridazinyl; 6-(S,R-2-hydroxymethyl-4-hydroxypyrrolidinyl)-3-pyridyl; 6-(R-2-hydroxymethyl-4-pyrrolidinyl)-3-pyridazinyl; 6-(1*S,4S*)-2-aza-5-oxa-bicyclo[2.2.1]heptane)-3-pyridyl; 6-(2-imidizolidone-1-yl)-3-pyridyl; 4-(2,4-(1*H*,3*H*)-quinazolinedion-3-yl)phenyl; 6-morpholinylcarboxamide-3-pyridazinyl; 6-methoxy-3-pyridazinyl; 6-N,N-diethoxyethylamino-3-pyridazinyl; 6-(4-ethoxymethylpiperidinyl)-3-pyridazinyl; 6-(4-tetrahydropyranyl methyl)piperidinyl)-3-pyridazinyl; 6-(4-ethoxyethoxymethylpiperidinyl)-3-pyridazinyl; 6-N-methyl-N-1,3-dioxalanemethylamino)-3-pyridazinyl; 6-(4,4-dioxyethylenecyclohexyloxy)-3-pyridazinyl; 6-dihydroxymethylmethoxy-3-pyridazinyl; 6-(3-pyridyloxy)-3-pyridazinyl; 4,7-epoxy-7-methyl-2,3,3*A*,4,5,6,7,7*a*-octahydro-1*H*-isoindolyl; 6-(4-N-methyl-N-methoxyethyl)-3-pyridazinyl; 6-(3,4-dimethoxymethoxypyrrolidinyl)-3-pyridazinyl; 6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl; 6-(*cis*-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl; 6-(*cis*-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl; 6-(trans-3-cyano-4-hydroxypyrrolidinyl)-3-pyridyl; 6-(3-hydroxy-4-tert-butylcarboxamidepyrrolidinyl)-3-pyridyl; 6-(S-2-(4-tetrahydropyranyloxy)methylpyrrolidinyl)-3-pyridazinyl; 6-(2-(4-

50

- 5

10 tetrahydropyranyloxy)iminopyrrolidinyl)-3-pyridazinyl; 2-morpholinyl-5-thiazoyl; 5-bromo-2-thienyl; 2,5-dimethyl-3-thienyl; 5-chloro-2-thienyl; 2,4-dimethyl-5-thiazoyl; 5-methyl-2-thienyl; 2-furanyl; 2-(4,4-dioxyethylenepiperidinyl)-5-thiazoyl; 3-thienyl; 3-methyl-2-thienyl; 2-morpholinyl-4-thiazoyl; 2-morpholinyl-4-trifluoromethyl-5-thiazoyl;

15 5-morpholinyl-2-thienyl; 4-methyl-2-morpholinyl-5-thiazoyl; 2,5-dichloro-3-thienyl; 2,5-dimethyl-3-furanyl; N-methyl-2-pyrrolyl; 2-N,N-dimethylamino-5-thiazoyl; 2-morpholinyl-5-thiazoyl; 2-(4,4-dioxythiomorpholinyl)-5-thiazoyl; 1-N-methyl-2-morpholinyl-5-imidazoyl; 2-morpholinyl-5-oxazolyl; 2-N-methyl-N-methoxyethylamino-5-thiazoyl; 2-N-methyl-N-ethylamino-5-thiazoyl; 2-N-pyrrolidinyl-5-thiazoyl; 2-N-methyl-N-propylamino-5-thiazoyl; 2-N,N-diethylamino-5-thiazoyl; 2-(N-methylpyperazinyl)-5-thiazoyl; 2-(N-(2-pyridyl)piperazinyl)-5-thiazoyl; 2-N-methyl-N-(2-pyridylethyl)-5-thiazoyl; 2-(4-oxopiperazinyl)-5-thiazoyl; 2-(4-(N-morpholinyl)iminopiperazinyl)-5-thiazoyl; 6-N-morpholine-3-pyridinesulfonamide; 2-(4-oxopiperidinyl)-5-pyrimidyl; 2-(4,4-dioxethylenepiperidinyl)-5-pyrimidyl; 5-(4,4-dioxethylenepiperidinyl)-2-pyrazinyl; 5-(4-oxopiperidinyl)-2-pyrazinyl; 6-N-cyclopropyl-3-pyridinesulfonamide; 6-N-(4,4-dioxethylenepiperidinyl)-3-pyridinesulfonamide; 2-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-5-pyrazinyl; 6-(4-(phenylmethoxy)iminopiperidinyl)-3-pyridyl; 6-(4-(tert-butyloxy)iminopiperidinyl)-3-pyridyl; 6-(4-(cyclohexyloxy)iminopiperidinyl)-3-pyridyl; 6-(4-hydroxyiminopiperidinyl)-3-pyridyl; 6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl; 6-(4-methoxyethoxyiminopiperidinyl)-3-pyridyl; 6-(4-(2-thenylmethoxy)iminopiperidinyl)-3-pyridyl; 6-(4-(1-(4-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridazinyl; 6-(4-(4'-acetyl-4'-hydroxypiperidinyl)-3-pyridazinyl; 6-(4-(1-(isopropylcaboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(ethylcaboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(methylcaboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(2-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(allyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(ethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-methoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-hydroxy)iminoethyl))-4-

5 hydroxypiperidinyl)-3-pyridyl; 6-(4-(2-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl;
10 6-(4-(isopropylcarboxymethoxy)iminopiperidinyl)-3-pyridyl; 6-(4-hydroxy-4-(1-(4-
tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(3-
butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(2-butyrolactone)-4-
5 hydroxypiperidinyl)-3-pyridazinyl; 6-(4-acetyl-4-hydroxypiperidinyl)-3-pyridyl; 6-(3-
hydroxyazetidinyl)-3-pyridyl; 6-(cis-3-hydroxytropanyl)-3-pyridyl; 6-(cis-2,3-
15 dihydroxypiperidinyl)-3-pyridyl; 6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridazinyl;
6-(1,2,3,6-tetrahydropyridyl)-3-pyridyl; 6-(4-(N-4'-methoxyphenylcarbamoyl)piperidinyl)-
3-pyridazinyl; 6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl; 6-(trans-3,4-bis(N-
20 4'-methoxyphenylcarbamoyl)pyrrolidinyl)-3-pyridyl; 6-(trans-3-hydroxytropanyl)-3-
pyridyl; 6-(S,S-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl; 6-(R,R-trans-3,4-
dihydroxypyrrolidinyl)-3-pyridazinyl; 6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl;
6-(8-(1-phenyl-1,3,8-triaza-2-spiro[4,5]deceN-4-one)-3-pyridyl; 6-(8-(1-phenyl-1,3,8-
25 triaza-2-spiro[4,5]deceN-4-one)-3-pyridyl; 6-(4-(2-keto-1-benzimidazolinyl)piperidinyl)-
3-pyridazinyl; 6-(4-oxothiomorpholinyl)-3-pyridyl; 6-(4-(2-keto-1-
benzimidazolinyl)piperidinyl)-3-pyridyl; 6-(N-methyl-N-(2-pyridylethyl)amino)-3-
30 pyridyl; 6-(N-methyl-N-(4-pyridylethyl)amino)-3-pyridyl; 6-N-(3-pyridylmethyl)amino-3-
pyridyl; 6-(2-hydroxymethylpiperidinyl)-3-pyridyl; 6-(4-hydroxy-4-(4-
bromophenyl)piperidinyl)-3-pyridyl; 6-(4-N-(2-pyridyl)piperazinyl)-3-pyridyl; 6-(4-N-
35 (2-hydroxyethoxyethyl)piperazinyl)-3-pyridyl; 6-(4,4-diacetoxyethylthio)piperidinyl)-3-
pyridyl; 6-(N-methy-N-(3-pyridylmethyl)amino)-3-pyridyl; 6-(4-pyrrolidinylpiperidinyl)-
3-pyridyl; 6-(4-N-cyanomethylpiperazinyl)-3-pyridyl; 6-(3-hydroxypyrroldinyl)-3-pyridyl;
6-(4-methylpiperidinyl)-3-pyridyl; 6-(cis-3,5-dimethylmorpholinyl)-3-pyridyl; 6-(4,4-
40 difluoropipridinyl)-3-pyridyl; 6-(4,4-dioxythiomorpholinyl)-3-pyridazinyl; 6-
25 thiazolidinyl-3-pyridyl; 6-(1,1-dioxythiazolidinyl)-3-pyridyl; 6-thiomorpholinyl-3-
pyridazinyl; 6-(2,5-dihydropyrrrolyl)-3-pyridyl; 6-hydroxy-3-pyridazinyl; 6-piperidinyl-3-
pyridyl; and 6-(4-tetrahydropyranyloxy)iminopyrrolidinyl-3-pyridyl; 6-morpholinyl-3-
5 pyridyl.

In another preferred embodiment, an adenosine kinase inhibitor of the present invention is a compound of Formula I above, wherein R³ is selected from the group

50 -20-

5

10

15

20

25

30

35

40

50

- consisting of: (thiophene-2-yl)methyl; (thiophene-3-yl)methyl; butyl; cycloheptyl; pentyl; thiophene-2-yl; 1-(3-bromophenyl)ethyl; 2-(N-phenylmethoxycarbonyl)aminophenyl; 2-(3-bromophenyl)ethyl; 2-(3-cyanophenyl)methyl; 2-(4-bromophenyl)ethyl; 2-(5-chloro-2-thiophen-3-yl)phenyl; 2-bromophenyl; 2-furanyl; 2-methylpropyl; 2-phenylethyl; phenylmethyl; 2,3-dimethoxyphenyl; 2,3-methylenedioxyphenyl; 3-(furan-2-yl)phenyl; 3-(thiophen-2-yl)phenyl; 3-(2-pyridyl)phenyl; 3-(3-methoxybenzyl)phenyl; 2-(3-aminopropynyl)phenylmethyl; 3-benzylxylophenyl; 3-bromo-4-fluorophenyl; 3-bromo-5-iodophenyl; 3-bromo-5-methoxyphenyl; 3-bromophenyl; 3-bromophenylmethyl; 3-carboxamidophenyl; 3-chlorophenyl; 3-cyanophenyl; 3-diethylmalonylallylphenyl; 3-dimethylaminophenyl; 3-ethoxyphenyl; 3-fluoro-5-trifluoromethylphenyl; 3-fluorophenyl; 3-hydroxyphenyl; 3-iodophenyl; 3-methoxyethoxyphenyl; 3-methoxyphenyl; 3-methylphenyl; 3-methylsulfonylphenyl; 3-methylthiophenyl; 3-t-butylacrylphenyl; 3-trifluoromethoxyphenyl; 3-trifluoromethylphenyl; 3-vinylpyridinylphenyl; 3,4-dichlorophenyl; 3,4-dimethoxyphenyl; 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; 3,5-di(trifluoromethyl)phenyl; 3,5-dibromophenyl; 3,5-dichlorophenyl; 3,5-dimethoxyphenyl; 3,5-dimethylphenyl; 4-(2-propyl)phenyl; 4-(2-propyl)oxyphenyl; 4-benzylxylophenyl; 4-bromophenyl; 4-bromothiophene-2-yl; 4-butoxyphenyl; 4-dimethylaminophenyl; 4-fluoro-3-trifluoromethylphenyl; 4-methoxyphenyl; 4-neopentylphenyl; 4-phenoxyphenyl; 5-bromothiophene-2-yl; 5-cyclohexyl; 5-cyclopropyl; 5-hexyl; 5-methyl; 5-phenyl; (2-bromo-5-chlorophenyl)methyl; (2-bromophenyl)methyl; (5-chloro-2-(3-methoxyphenyl)phenyl)methyl; 3-bromophenyl; 2-pyridyl; 2-ethoxyphenyl; 5-ethoxyphenyl; 2,5-dichlorophenyl; 2,5-dimethylphenyl; 3-fluorophenyl; 3-trifluoromethylphenyl; 5-trifluoromethylphenyl; 3,5-diclorophenyl; 4-bromo-2-thienyl; 3-bromo-2-thienyl; 3-cyanophenyl; 4-tetrahydropyranyl; 3-indolyl; 5-indolyl; 4-quinolyl; 2-bromophenyl; 4-fluorophenyl; 4,4-difluorocyclohexyl; 1,1-dimethyl-3-butetyl; 2,3-dichlorophenyl; isopropyl; and 2-trifluorophenylphenyl.

Exemplary and preferred adenosine kinase inhibitor compounds of the invention utilized in the method recited herein include the compounds listed below wherein R¹, R², R³, and R⁴ are as described in Formula I in the specific compound:

- 5 4-(N-(2,3-dihydroxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,
- 10 4-(N-(3-morpholinylpropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,
- 5 4-(N-(2-(4-imidazolyl)ethyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,
- 15 4-(N-(3-carboxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,
- (S)-4-amino-5-(3-bromophenyl)-7-(6-(O-methyl-2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,
- 20 (S)-4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,
- 25 4-amino-5-(4-fluorophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine,
- 30 4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazolyl)pyrido[2,3-d]pyrimidine,
- 35 4-amino-5-(N-methyl-3-indolyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,
- 40 4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxycarbonylmethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,
- 45 4-amino-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine.

50

5

4-amino-5-(4-dimethylaminophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(4-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

15

4-amino-5-(4-dimethylaminophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(4-neopentylphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(4-butoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(4-(2-propyl)oxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(4-butoxyphenyl)-7-(4-N-formylpiperazinylphenyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(4-benzyloxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(4-phenoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(4-(2-propyl)phenyl)-7-(4-diethylmalonylallylphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(4-(2-propyl)phenyl)-7-(4-t-butylacylphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3,4-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-t-butylacrylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

40

4-amino-5-(3-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

45

4-amino-5-(3-diethylmalonylallylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-vinylpyridinylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

50

5

4-amino-5-(3-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(3-carboxamidophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

15

5 4-amino-5-(3-cyanophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-benzyloxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

20

10 4-amino-5-(3-(2-pyridyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-methylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-chlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

15 4-amino-5-(3-bromophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-bromophenyl)-7-phenylpyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-ethylphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,

20 4-amino-5-(3-bromophenyl)-7-(4-cyanophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-hydroxyphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-iodophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-ethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

45 4-amino-5-(3-trifluoromethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3,5-dichlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

40

45 4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

30 50 4-amino-5-(3-hydroxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

5

4-amino-5-(3-bromophenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-piperidinylphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(imidazol-1-yl)phenyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(3-bromophenyl)-7-(4-chlorophenyl)pyrido[2,3-d]pyrimidine,

5

4-amino-5-(3-bromophenyl)-7-(4-isopropylphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-trifluorophenyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(3,4,5-trimethoxyphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-(3-methoxybenzyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

10 d]pyrimidine,

20

4-amino-5-(3-methoxyethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3,4-methylenedioxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(4-ethoxyphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2'-thiophene)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-bromophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-dimethylaminophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

20 4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3,4,5-trimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine,

40

25 4-amino-5-(3-bromophenyl)-7-(3,4-methylenedioxyphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(thiophen-2-yl)-7-(4-morpholinylphenyl)pyrido [2,3-d]pyrimidine,

45

4-amino-5-(3,5-dimethoxyphenyl)-7-(thiophen-2-yle)pyrido [2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-carboxamidophenyl)pyrido[2,3-d]pyrimidine,

50

5

4-amino-5-(3-bromophenyl)-7-(4-(2-methoxyethoxyphenyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine,

5 4-amino-5-(3-trifluoromethylphenyl)-7-(thiophene-2-yl)pyrido [2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromo-4-fluorophenyl)-7-(thiophene-2-yl)pyrido [2,3-d]pyrimidine.

4-amino-5-(3-bromo-4-fluorophenyl)-7-(2-furanyl)pyrido [2,3-d]pyrimidine,

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine,

20

10 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-imidazolylphenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(thiophene-2-yl)phenyl)pyrido[2,3-

d]pyrimidine,

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(3-pyridyl)phenyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(4-(4-methylpiperidinyl)phenyl)pyrido[2,3-

15 d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(4-bromothiophene-)-7-(4-dimethylaminophenyl)pyrido[2,3-

d]pyrimidine,

4-amino-5-(4-bromothiophene-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-

20 d]pyrimidine,

4-morpholinyl-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

d]pyrimidine,

4-amino-5-(5-bromothiophene-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-

d]pyrimidine,

40

25 4-amino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(acetylamino)phenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(3,5-dimethoxyphenyl)-7-(5-pyrimidinylphenyl)pyrido[2,3-

d]pyrimidine,

50

5

4-(4-fluorophenyl)amino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(4-bromothiophene-2-yl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine.

15

4-amino-5-(4-bromothiophene-2-yl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(5-(dimethylamino)thiophene-2-yl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromo-5-iodophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3,5-di(trifluoromethyl)phenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3,5-dibromophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3,5-dibromophenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(4-bromothiophene-2-yl)-7-(4-(4-methylpiperidinyl)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3,5-dibromophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-bromophenyl)-7-(3-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(3-methoxyphenyl)pyrido[2,3-d]pyrimidine,

40

4-amino-5-(3-bromophenyl)-7-(4-(methylthio)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-methylaminophenyl)pyrido[2,3-d]pyrimidine,

50

4-amino-5-(3-bromophenyl)-7-(4-methylaminophenyl)pyrido[2,3-d]pyrimidine,

55

5

4-amino-5-(3-bromophenyl)-7-(3-amino-4-methoxyphenyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(3-bromophenyl)-7-(3-bromo-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine,

5

4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-trifluoroacetylamino)phenyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(3-bromophenyl)-7-(4-(dimethylamino)-3-fluorophenyl)pyrido[2,3-

20

d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-(N-ethyl-N-formylamino)phenyl)pyrido[2,3-

d]pyrimidine.

25

4,4-bis(acetylamino)-5-(3-bromophenyl)-7-(4-(N-methyl-N-acetylaminophenyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(4-(N-acetyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(N-ethylamino)phenyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(4-(N-isopropylamino)phenyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-bromophenyl)-7-(4-N-ethyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-N-(3-methoxypropionyl)-N-isopropyl-

40

amino)phenyl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(3-bromophenyl)-7-(4-N-(2-(dimethylamino)ethyl)-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(N-(2-(dimethylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine,

50

5

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-cyano)ethylamino)phenyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(3-methoxy)propionylamino)phenyl)pyrido[2,3-d]pyrimidine,

5 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-formyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methylamino)phenyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(4-(4-methoxy-2-butyl)phenyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-(N-phthalimidyl)acetyl)amino)phenyl)pyrido[2,3-d]pyrimidine,

15 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methyl-N-(trifluoroacetyl)amino)phenyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-acetyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridinyl)pyrido[2,3-d]pyrimidine,

40

4-amino-5-(3-cyanophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine,

20 4-amino-5-(3-cyanophenyl)-7-(4-(N-methyl-N-formylamino)-phenyl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-formylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

50

4-amino-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,

25 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methoxyethylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

55

4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2-(dimethylamino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine,

30 d]pyrimidine,

- 5 4-amino-5-(3-bromophenyl)-7-(2-(N-methoxyethyl-N-methyl amino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine.
- 10 4-amino-5-(3-bromophenyl)-7-(2-(N-formyl-N-methyl amino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine.
- 15 4-amino-5-(3-bromophenyl)-7-(2-(N-methylamino)5-pyrimidinyl)pyrido[2,3-d]pyrimidine,
- 20 4-amino-5-(3-bromophenyl)-7-(2-(1-pyrrolidinyl)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine,
- 25 4-amino-5-(3-bromophenyl)-7-(6-(2-oxo-3-oxazolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,
- 30 4-amino-5-(3-bromophenyl)-7-(2-pyridyl)pyrido[2,3-d]pyrimidine,
- 35 4-amino-5-(3-bromophenyl)-7-(3-pyridyl)pyrido[2,3-d]pyrimidine,
- 40 4-amino-5-(3-(thiophen-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 45 4-amino-5-(3-(furan-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 50 4-amino-5-(3-(3-methoxyphenyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.
- 4-amino-5-(3-chlorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-chlorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-chlorophenyl)-7-(4-(thiophen-2-yl)phenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-chlorophenyl)-7-(4-(5-pyrimidinyl)phenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(4-bromothiophene-2-yl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine.

5

4-amino-5-(3-bromophenyl)methyl-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(2-phenylethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(2-methylpropyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

5

4-amino-5-(butyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(2-(4-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(butyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(2-(3-cyanophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

10 d]pyrimidine,

20

4-amino-5-(2-(N-phenylmethoxycarbonyl)aminoethyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(cycloheptyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(2-(5-chloro-2-(thiophen-3-yl)phenyl)methyl)-7-(4-

15 dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(pentyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-hexyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(2-(3-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(2-(3-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

35

20 4-amino-5-((2-bromophenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-cyclopropyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-cyclohexyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

40

4-amino-5-((2-bromo-5-chlorophenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

25 d]pyrimidine,

4-amino-5-methyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(2,3-methylenedioxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

d]pyrimidine,

4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(4-

50 30 dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

5

4-amino-5-(2-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3,5-dimethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(3,4-dichlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

5 d]pyrimidine,

4-amino-5-(4-fluoro-3-trifluoromethylphenyl)-7-(4-

15

dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine,

20

10 4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-piperidinylphenyl)pyrido[2,3-d]pyrimidine,

25

15 4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-methylthiophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

30

4-amino-5-(3-bromo-5-methoxyphenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine,

4-amino-5-(2,3-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-methylsulfonylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-acetylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

40

25 4-formylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-(methoxyacetyl)amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine.

45

4-trifluoroacetylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

30 30 d]pyrimidine,

50

5

4-pentanoylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

10

4-benzoylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

5

4-(N-BOC-glycyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

15

4-(N-phthalimidylglycyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

20

4-(ethoxycarbonyl)amino-5-(3-bromophenyl)-7-(4-

dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-(ethylaminocarbonyl)amino-5-(3-bromophenyl)-7-(4-

dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-allylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl) pyrido[2,3-d]pyrimidine,

25

4-(2-(N,N-dimethylamino)ethylamino)-5-(4-bromophenyl)-7-(4-dimethylaminophenyl) pyrido[2,3-d]pyrimidine,

30

4-(4-(N,N-dimethylamino)butylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl) pyrido[2,3-d]pyrimidine,

35

4-(N-allyl-N-formylamino)-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,

4-diacetylamino-5-(p-dimethylaminophenyl)-7-(4-

bromophenyl)pyrido[2,3-d]pyrimidine,

40

4-amino-5-(3-bromophenyl)-7-(5-amino-2-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-

pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-

pyrazinyl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(3-bromophenyl)-7-(2-oxobenzoxazolin-6-yl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(1-methyl-2-oxobenzoxazolin-6-

yl)pyrido[2,3-d]pyrimidine.

50

5

- 4-amino-5-((5-chloro-2-(3-methoxyphenyl)phenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-((thiophene-2-yl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-((thiophene-3-yl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-((2-bromophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(4-(N-formyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(4-(N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-dimethylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(4-(2-methoxyacetylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-((4-formylamino)phenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)acetylamino)phenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(4-(2-oxo-3-oxazolidinyl)phenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-(2-propyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-phenylmethyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(2-(3-aminopropynyl)phenylmethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(1-(3-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

50

5

4-amino-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(2-furanyl)-7-(4-(N-morpholinyl)phenyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(3-bromophenyl)-7-(2-dimethylamino-5-pyrimidinyl)pyrido[2,3-d]pyrimidine.

5

4-amino-5-(3-bromophenyl)-7-(4-(ureido)phenyl)pyrido[2,3-d]pyrimidine.

15

4-amino-5-(1-phenylmethyl-3-piperidinyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(3-methyl-5-isoxazolyl))-3-pyridinyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(6-chloro-3-pyridinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-methoxy-3-pyridinyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(6-(1,2,4-triazol-4-yl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-pyrimidinyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(2-thiazolyl)-7-(4-pyrrolidinylphenyl)-pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-pyrazolyl-3-pyridinyl)-pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-ureido)phenyl)-pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-methylamino)phenyl)-

40

pyrido[2,3-d]pyrimidine,

4-formylamino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-methylamino)phenyl)-

45

pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-methylsulfonylamino)phenyl)pyrido[2,3-d]pyrimidine.

50

5

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methylsulfonylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(3-bromophenyl)-7-(1-methyl-5-indolinyl)pyrido[2,3-d]pyrimidine.

15

4-amino-5-(3-bromophenyl)-7-(1-methyl-5-benzimidazolyl)pyrido[2,3-

d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-pyrazinyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(5-(N-(2-methoxyethyl)-N-methylamino)-2-

pyrazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(morpholinylmethyl)-phenyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-bromophenyl)-7-(5-(N,N-bis(2-methoxyethyl)amino)-2-pyridinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(imidazolylmethyl)-phenyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-bromophenyl)-7-(5-(1-morpholinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-((dimethylamino)methyl)-phenyl)pyrido[2,3-

40

d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(5-(4-hydroxy-1-piperidinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(3-bromophenyl)-7-(5-(N-formyl-N-methylamino)-2-

pyridinyl)pyrido[2,3-d]pyrimidine.

50

5

4-amino-5-(3-bromophenyl)-7-(5-(2-propenyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(3-bromophenyl)-7-(3-(2-methoxyethyl)-2-oxo-6-benzoxazolyl)pyrido[2,3-d]pyrimidine.

5

4-amino-5-(3-bromophenyl)-7-(4-(1-(N-formylamino)-ethyl)phenyl)pyrido[2,3-d]pyrimidine,

15

4-(methylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine hydrochloride;

20

4-(2-methoxyethylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine hydrochloride;

4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-2-imidazolyl)phenyl)pyrido[2,3-d]pyrimidine trihydrochloride;

4-amino-5-(3-bromophenyl)-7-(4-(aminomethyl)phenyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(2-bromo-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(4-(dimethylaminoethyl)phenyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-bromophenyl)-7-(4-(3-(dimethylamino)propynyl)phenyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(4-(3-amino-3-methylbutynyl)phenyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-bromophenyl)-7-(4-dimethylphosphonatophenyl)pyrido[2,3-d]pyrimidine,

40

4-amino-5-(3-bromophenyl)-7-(4-(3-methoxypropynyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(4-carboxyphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)ethyl)-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine.

50

5

- 4-amino-5-(3-bromophenyl)-7-(2,3-dihydro-3-(dimethylaminoethyl)-2-oxobenzoxazol-6-yl)pyrido[2,3-d]pyrimidine.
- 4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(2,2,4-trimethyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-cyclohexyl-7-(4-(2-dimethylamino)ethyl)-2H-4H-benzo-3-oxo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(5-(1-methylethyl)-2-pyridyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(5-piperidin-1-ylpyrid-2-yl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(1-(4-bromophenyl)ethyl)-7-(6-morpholinylpyrid-3-yl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(4-((N-formylamino)methyl)phenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-1-(N-methylamino)ethyl)phenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(4-(1-(dimethylamino)-1-methylethyl)phenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(N-acetyl-5-indolinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-cyclohexyl-7-(6-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-diethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(4-(N-methyl-N-formyl)amino)phenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-cyclohexyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

50

5

4-amino-5-((2-bromophenyl)methyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(4-tetrahydropyranyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

15

5 4-amino-5-cyclohexyl-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine,
4-amino-5-(1-ethylpropyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine,
4-amino-5-cyclopentyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,
4-amino-5-cyclohexyl-7-(2-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine,
4-amino-5-(3,5-dimethylcyclohexyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-

20

10 d]pyrimidine,
4-amino-5-((N-(benzyloxycarbonyl)-4-piperidinyl)methyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-cyclohexyl-7-(6-bromo-3-pyridyl)pyrido[2,3-d]pyrimidine,

15 4-amino-5-cyclohexyl-7-(3-cyanophenyl)pyrido[2,3-d]pyrimidine,
4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-dimethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

30

30 4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

20 4-amino-5-(3-bromophenyl)-7-(6-(azacycloheptanyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(1-methylethyl))amino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

40

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

25 4-amino-5-cyclohexyl-7-(6-(4-acetyl(piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-cyclohexyl-7-(6-(4-acetyl-1,4-diazacycloheptanyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

30 4-amino-5-cyclohexyl-7-(6-(4-methyl-1,4-diazacycloheptanyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

50

5

4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(2-(2-pyridyl)ethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-cyclohexyl-7-(6-2-(N,N'-dimethylaminoethyl)-N-methylamino)-3-pyridyl)pyrido[2,3-d]pyrimidine,

5 4-amino-5-cyclohexyl-7-(6-azetidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

15

4-amino-5-cyclohexyl-7-(6-(3-(N-methylacetamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-cyclohexyl-7-(6-(3-(formamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-cyclohexyl-7-(6-(2-methoxymethyl)pyrrolidin-1-yl)pyridyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-cyclohexyl-7-(6-(N-methoxyethyl-N-propylamino)pyridyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-cyclohexyl-7-(N-methyl-N-(2,2-dimethoxyethyl)amino)pyrido[2,3-d]pyrimidine,

4-amino-5-cyclohexyl-7-(6-(4-(dimethylamino)piperidinyl)pyridyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-cyclohexyl-7-(6-(4-(aminocarbonyl))piperidinyl)pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-cyclohexyl-7-(N-methyl-N-(3-(diethylamino)propyl)aminopyrid-3-yl)pyrido[2,3-d]pyrimidine,

40

4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(4-pyridyl)ethylamino)pyrid-3-yl)pyrido[2,3-d]pyrimidine,

4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(3-pyridylmethylamino)pyrid-3-yl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-5-indolyl)pyrido[2,3-d]pyrimidine,

50

5

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-2,3-dioxo-5-indolyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(1-morpholinyl)phenyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(4-hydroxy-3-nitrophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-

pyridyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperazinyl)-3-pyridyl)pyrido[2,3-

d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(6-(4-formylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(2-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromo-4-methoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

20 d]pyrimidine.

35

4-amino-5-(4-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-chlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(5-chloro-6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

40

4-amino-5-(3-bromophenyl)-7-(6-(N-oxidomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)amino)-3-

45

pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-N-formylamino)-3-

30 pyridyl)pyrido[2,3-d]pyrimidine,

50

5

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-3-pyridyl-N-oxide)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxy)morpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

15

5 1-(5-(4-amino-5-(3-bromophenyl)pyrido[2,3-d]pyrimidin-7-yl)-2-pyridyl)-piperidine-4-phosphate, disodium salt;

20

4-amino-5-(3-bromophenyl)-7-(4-methylen(piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(4-hydroxy-4-(hydroxymethyl)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

30

4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

35

4-amino-5-cyclohexyl-7-(6-(4-oxo-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

40

4-amino-5-cyclohexyl-7-(6-(4-methylen(piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

45

4-allylamino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl) pyrido[2,3-d]pyrimidine,

50

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

55

4-amino-5-(cyclohexyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

60

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazolyl)pyrido[2,3-d]pyrimidine,

65

4-(N-(2,3-dihydroxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,

70

4-(N-(3-morpholinylpropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine.

5

4-(N-(2-(4-imidazolyl)ethyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,

10

4-(N-(3-carboxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,

5 (S)-4-amino-5-(3-bromophenyl)-7-(6-(O-methyl-2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

15

(S)-4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(4-fluorophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine,

15 4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazolyl)pyrido[2,3-d]pyrimidine.

35

4-amino-5-(N-methyl-3-indolyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,

40

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

25 4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

30 4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridazyl)pyrido[2,3-d]pyrimidine.

50

5

- 4-amino-5-(3-bromophenyl)-7-(6-(4-methoxyiminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-phenylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine.
- 4-amino-5-(3-bromophenyl)-7-(6-(4-methoxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-isobutoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-(4-tetrahydropyranyloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-morpholinylethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-(4-tetrapyranyloxyethyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-(3-(R)-tetrahydrofuranyloxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-(3-(S)-tetrahydrofuranyloxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

50

- 5 4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine.
- 10 4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.
- 15 5 4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.
- 20 10 4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 25 15 4-amino-5-(3-bromophenyl)-7-(6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 30 20 4-amino-5-(3-bromophenyl)-7-(6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 35 25 4-amino-5-(2-pyridyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 40 30 4-amino-5-(2,3-dichlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 45 35 4-amino-5-(2-pyridyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 40 4-amino-5-(2-ethoxyphenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 45 4-amino-5-(2-bromo-5-ethoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 50 4-amino-5-(2,5-dichlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 55 4-amino-5-(2,5-dimethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine
- 60 25 4-amino-5-(3-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 65 4-amino-5-(3-trifluoromethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 70 4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

- 5 4-amino-5-(3,5-diclorophenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine.
- 10 4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxa-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 15 5 4-amino-5-(4-bromo-2-thienyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 20 4-amino-5-(3-bromophenyl)-7-(6-(4-tertbutyl)piperidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 25 4-amino-5-(3-bromophenyl)-7-(6-(4-N-formyl)piperidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 30 10 4-amino-5-(3-bromo-2-thienyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 35 15 4-amino-5-(3-cyanophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 40 20 4-amino-5-(3-Bromophenyl)-7-(6-(S-O-ethyl-2-hydroxymethylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 45 25 4-amino-5-(3-bromophenyl)-7-(6-((2S,3S)-2,3-dimethyl-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 50 30 4-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-1,2-dioxycyclopentyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 55 35 4-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-1-oxa-4,8-diazaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 60 40 4-amino-5-(3-bromophenyl)-7-(6-((2R,3R)-2,3-bis(methoxymethyl)-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 65 45 4-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-3,4-dioxy-oxacyclopentyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 70 50 4-amino-5-(3-bromophenyl)-7-(6-(3-methoxy-1,5-dioxa-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 75 55 4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxa-3-hydroxymethyl-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

- 5 4-amino-5-(3-bromophenyl)-7-(6-(1,7,14-trioxa-11-azadispiro[4.2.5.2]pentadecan-11-yl)-
10 3-pyridazinyl)pyrido[2,3-d]pyrimidine,
10 4-amino-5-(4-tetrahydropyranyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-
d]pyrimidine,
5 4-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridyl)pyrido[2,3-
d]pyrimidine,
15 4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-
pyridyl)pyrido[2,3-d]pyrimidine,
15 4-amino-5-(3-bromophenyl)-7-(6-(4-(1,2,4-triazol-1-yl)iminopiperidinyl)-3-
pyridyl)pyrido[2,3-d]pyrimidine,
20 4-amino-5-(3-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,
4-amino-5-(5-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.
25 4-amino-5-(3-bromophenyl)-7-(6-(4-ethylpiperidinylcarboxylate)-3-pyridyl)pyrido[2,3-
d]pyrimidine,
15 4-amino-5-(3-bromophenyl)-7-(2-phenylmethyl-3(2H)-pyridazinone-6-yl)pyrido[2,3-
d]pyrimidine,
30 4-amino-5-(3-bromophenyl)-7-(6-(4-(morpholinylcarboxamide)piperidinyl)-3-
pyridyl)pyrido[2,3-d]pyrimidine,
4-amino-5-(3-bromophenyl)-7-(6-(4-(N-morpholinylaminocarboxamide)piperidinyl)-3-
20 pyridyl)pyrido[2,3-d]pyrimidine,
35 4-amino-5-(3-bromophenyl)-7-(6-(4-(N,N-dimethylaminocarboxamide)piperidinyl)-3-
pyridyl)pyrido[2,3-d]pyrimidine,
4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methyl-N-methoxyethylcarboxamide)piperidinyl)-3-
40 pyridyl)pyrido[2,3-d]pyrimidine,
25 4-amino-5-(4-quinolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,
4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methoxyethylcarboxamide)piperidinyl)-3-
pyridyl)pyrido[2,3-d]pyrimidine,
45 4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxymethylpiperidinyl)-3-pyridyl)pyrido[2,3-
d]pyrimidine.

5

4-amino-5-(2-bromophenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

15

5 4-amino-5-(3-bromophenyl)-7-(6-(4-N-acetyl(piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-cyanopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

20

4-amino-5-(3-bromophenyl)-7-(6-(4-N-(4-fluorophenyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

10 4-amino-5-(4-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-morpholinylbenzenesulfonamide)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(4-N-1,4-dioxa-8-azaspiro[4.5]decan-8-ylbenzenesulfonamide)pyrido[2,3-d]pyrimidine,

15 4-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylbenzenesulfonamide)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-piperidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-bromophenyl)-7-(4-(4-cyanopiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine,

20 4-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylmethylbenzenesulfonamide)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-bromophenyl)-7-(4-N,N-dimethylaminobenzensulfonamide)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-N-(S)-2-

40

25 hydroxymethylpyrrolidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(3-bromophenyl)-7-(4-(cis-3,5-dimethylmorpholinyl)benzenesulfonamide)pyrido[2,3-d]pyrimidine.

50

- 5 4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-thiomorpholinylphenyl)pyrido[2,3-d]pyrimidine.
- 10 4-amino-5-(4-fluorophenyl)-7-(6-(thiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 15 4-amino-5-(4-fluorophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 20 4-methoxy-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 25 4-amino-5-(3-bromophenyl)-7-(4-(4-dioxa-8-azaspiro[4.5]decan-8-ylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine,
- 30 4-amino-5-(3-bromophenyl)-7-(4-(N-cyclopropylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine,
- 35 4-amino-5-(3-bromophenyl)-7-(4-(morpholinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine,
- 40 4-amino-5-(3-bromophenyl)-7-(6-N-cyclopropylamino-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 45 4-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine,
- 50 4-amino-5-(3-bromophenyl)-7-(6-(S)-hydroxymethylpyrrolidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 55 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 60 4-amino-5-(3-bromophenyl)-7-(6-hexahydropyrimidine-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 65 4-amino-5-(4,4-difluorocyclohexyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 70 4-amino-5-(3-bromophenyl)-7-(6-(S)-2-ethoxyethoxypyrrolidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 75 4-amino-5-(3-bromophenyl)-7-(6-(R)-2-ethoxyethoxypyrrolidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 80 4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

5

4-amino-5-(3-bromophenyl)-7-(6-((3aR,6aS)-2-oxo-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

5 4-amino-5-(3-bromophenyl)-7-(6-(S,R-2-hydroxymethyl-4-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(6-(R-2-hydroxymethyl-4-pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(6-(2-imidizolidone-1-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(1,1-dimethyl-3-butenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,
4-amino-5-(3-bromophenyl)-7-(6-(2,4-dioxo-(1H,3H)-quinazolin-3-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

35

15

4-amino-5-(3-bromophenyl)-7-(6-carboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
4-amino-5-(3-bromophenyl)-7-(6-morpholinylcarboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

40

4-amino-5-(3-bromophenyl)-7-(6-methoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

20 4-amino-5-(3-bromophenyl)-7-(6-N,N-diethoxyethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

45

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxymethylpiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

25 4-amino-5-(3-bromophenyl)-7-(6-(4-tetrahydropyranoxymethyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyethoxymethylpiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

50

4-amino-5-(3-bromophenyl)-7-(6-N-methyl-N-1,3-dioxolanemethylamino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

- 5 4-amino-5-(3-bromophenyl)-7-(6-(1,4-dioxaspiro[4.5]decanyl-8-oxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine.
- 10 4-amino-5-(3-bromophenyl)-7-(6-dihydroxymethylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 15 5 4-amino-5-(3-bromophenyl)-7-(6-(3-pyridyloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
 4-amino-5-(3-bromophenyl)-7-(6-(4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
 4-amino-5-(3-bromophenyl)-7-(6-(4-N-ethyl-N-methoxyethyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 20 10 4-amino-5-(3-bromophenyl)-7-(6-(4-N-methyl-N-methoxyethyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
 4-amino-5-(3-bromophenyl)-7-(6-(3,4-dimethoxymethoxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 25 15 4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
 4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 30 30 4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 35 20 4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
 4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
 4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 40 45 4-amino-5-(3-bromophenyl)-7-(6-(trans-3-cyano-4-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
 4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxy-4-tert-butylcarboxamidepyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

50

5

4-amino-5-(3-bromophenyl)-7-(6-(S-2-(4-tetrahydropyranyloxy)methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydropyranyloxy)iminopyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

15

5 4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(5-bromo-2-thienyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-thienyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(5-chloro-2-thienyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2,4-dimethyl-5-thiazoyl)pyrido[2,3-d]pyrimidine,

20

10 4-amino-5-(3-bromophenyl)-7-(5-methyl-2-thienyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2-furanyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-5-thiazoyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(3-thienyl)pyrido[2,3-d]pyrimidine,

15 4-amino-5-(3-bromophenyl)-7-(3-methyl-2-thienyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazoyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-trifluoromethyl-5-thiazoyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-thienyl)pyrido[2,3-d]pyrimidine,

35

20 4-amino-5-(3-bromophenyl)-7-(4-methyl-2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2,5-dichloro-3-thienyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-furanyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(N-methyl-2-pyrrolyl)pyrido[2,3-d]pyrimidine,

40

25 4-amino-5-(3-bromophenyl)-7-(2-N,N-dimethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(3-bromophenyl)-7-(2-(4,4-dioxythiomorpholinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine,

50

- 5 4-amino-5-(3-bromophenyl)-7-(2-(1,1-dioxidothiomorpholinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine,
- 10 4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-oxazoyl)pyrido[2,3-d]pyrimidine.
- 15 4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-methoxyethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine,
- 20 4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-ethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine,
- 25 4-amino-5-(3-bromophenyl)-7-(2-N-pyrrolidinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine,
- 30 4-amino-5-(3-bromophenyl)-7-(2-(N-methyl-N-propylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine,
- 35 4-amino-5-(3-bromophenyl)-7-(2-(N-(2-pyridyl)piperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine,
- 40 4-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine,
- 45 4-amino-5-(3-bromophenyl)-7-(2-(4-(N-morpholinyl)iminopiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine,
- 50 4-amino-5-(3-bromophenyl)-7-(6-N-morpholine-3-pyridinesulfonamide)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperidinyl)-5-pyrimidyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(5-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-2-pyrazinyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(3-bromophenyl)-7-(5-(4-oxopiperidinyl)-2-pyrazinyl)pyrido[2,3-d]pyrimidine.

5

4-amino-5-(3-bromophenyl)-7-(6-N-cyclopropyl-3-pyridinesulfonamide)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(3-bromophenyl)-7-(6-(N-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridylsulfonamide)pyrido[2,3-d]pyrimidine.

15

5 4-amino-5-(3-bromophenyl)-7-(2-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-5-pyrazinyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(6-(4-(phenylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(6-(4-(tert-butyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-bromophenyl)-7-(6-(4-(cyclohexyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxyiminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

40

15 4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

45

4-amino-5-(3-bromophenyl)-7-(6-(4-methoxyethoxyiminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

50

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-thenylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

55

20 4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-(5'H-2-oxyfuranyl)-4-hydroxy)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

60

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(4-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

65

25 4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-acetyl-4'-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

70

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(isopropylcaboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

75

45 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethylcaboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

80

- 5 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 10 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(2-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 15 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(allyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 20 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 25 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 30 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(hydroxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 35 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 40 4-amino-5-(3-bromophenyl)-7-(6-(4-(isopropylcarboxymethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 45 4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxy-4-(1-(4-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 50 4-amino-5-(3-bromophenyl)-7-(6-(4-(3-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 55 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 60 4-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 65 4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxyazetidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 70 4-amino-5-(3-bromophenyl)-7-(6-((1R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 75 4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

5

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(3-bromophenyl)-7-(6-(1,2,3,6-tetrahydropyridyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

15

5 4-amino-5-(3-bromophenyl)-7-(6-(4-(N-4'-methoxyphenylcarbamoyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis(N-4'

10 methoxyphenylcarbamoyl)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-((1S,5R)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(S,S-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

15 4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)-3-

20 pyridyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-oxo-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4,4-dioxido-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

40

25 4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazolinyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(3-bromophenyl)-7-(6-(4-oxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

30 50 4-amino-5-(3-bromophenyl)-7-(6-(4-oxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

- 5 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazolinyl)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 10 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(2-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 15 5 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(4-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 20 4-amino-5-(3-bromophenyl)-7-(6-N-(3-pyridylmethyl)amino-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 25 4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 30 4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 35 4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxy-4-(4-bromophenyl)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 40 15 4-amino-5-(3-bromophenyl)-7-(6-(4-N-(2-pyridyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 45 4-amino-5-(3-bromophenyl)-7-(6-(4-N-(2-hydroxyethoxyethyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 50 4-amino-5-(3-bromophenyl)-7-(6-(4,4-diacetoxyethylthio)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 55 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 60 4-amino-5-(3-bromophenyl)-7-(6-(4-pyrrolidinylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 65 25 4-amino-5-(3-bromophenyl)-7-(6-(2-(1H-imidazol-4-yl)ethylamino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,
- 70 4-amino-5-(3-bromophenyl)-7-(6-(4-N-cyanomethylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,
- 75 4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

5

4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(3-bromophenyl)-7-(6-(cis-3,5-dimethylmorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

5

4-amino-5-(3-bromophenyl)-7-(6-(4,4-difluoropipridinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidothiomorpholinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-thiazolidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidothiazolidin-3-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(6-(2,5-dihydropyrrolyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(6-(1,3-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-bromophenyl)-7-(6-hydroxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

amino-5-(2,3-dichlorophenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-

20

pyridyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-isopropyl-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-piperidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

40

4-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydropyranyloxyimino)pyrrolidinyl)-3-

25

pyridyl)pyrido[2,3-d]pyrimidine, and

4-amino-5-(2-trifluorophenylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-

d]pyrimidine and pharmaceutically acceptable salts and amides thereof. In addition, the

45

partially hydrogenated or fully hydrogenated versions wherein the 5,6 and/or the 7,8 double bonds are hydrogenated of the compounds identified above are also included

30 within the scope of the invention. The preferred substitution pattern on the R³ group when

50

5

10

15

20

25

it is selected from, for example, a substituted aryl group, is having at least one substituent at the meta position. The preferred substitution pattern on the R⁴ position when it is selected from, for example, a substituted heterocycle or aryl group, is having at least one substituent at the para position. The present invention is therefore directed to compounds of formula I or II with the variables recited as above wherein, in the case of R³ selected from substituted aryl or heterocycle groups and R⁴ selected from substituted aryl or heterocycle groups, the substituents on the R³ group are meta and the substituents on the R⁴ group are para. In addition, the present invention encompasses pro-drugs of the above compounds which may be active in their own right or are metabolized or converted to the non pro-drug form as exemplified above. The invention is not limited to synthetic versions of the claimed compounds and includes the compounds-per-se or pro-drugs or metabolites thereof regardless of how or where they are manufactured or made.

Definitions of Terms

- 15 The term "alkenyl," as used herein, refers to a straight or branched chain hydrocarbon containing from 2 to 6 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-but enyl, 4-pentenyl, 5-hexenyl, and the like.
- 20 The term "alkenyloxy," as used herein, refers to an alkenyl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of alkenyloxy include, but are not limited to, 2-propenyloxy, 2-methyl-2-propenyloxy, 3-butenyloxy, 4-pentenyloxy, and the like.
- 25 The term "alkenyloxyimino," as used herein, refers to an alkenyloxy group, as defined herein, appended to the parent molecular moiety through an imino moiety, as defined herein. Representative examples of alkenyloxyimino include, but are not limited to, 2-propenyloxyimino, 2-methyl-2-propenyloxyimino, 3-butenyloxyimino, 4-pentenyloxyimino, and the like.
- 30 The term "alkenyloxyiminoalkyl," as used herein, refers to an alkenyloxyimino group, as defined herein, appended to the parent molecular moiety through an alkyl group,

50

55

5

as defined herein. Representative examples of alkenyloxyiminoalkyl include, but are not limited to, propen-2-yloxyiminomethyl, 2-[2-methylpropen-2-yloxyimino]ethyl, 2-[buten-3-yloxyimino]ethyl, 3-[penten-4-yloxyimino]propyl, and the like.

10

The term "alkoxy," as used herein, refers to an alkyl group, as defined herein,

5 appended to the parent molecular moiety through an oxy moiety, as defined herein.

15

Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy and the like.

20

The term "alkoxyalkoxy," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through another alkoxy group, as defined herein. Representative examples of alkoxyalkoxy include, but are not limited to, tert-butoxymethoxy, 2-ethoxyethoxy, 2-methoxyethoxy, methoxymethoxy, and the like.

25

The term "alkoxyalkoxyalkyl," as used herein, refers to an alkoxyalkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyalkoxyalkyl include, but are not limited to, 2-(tert-butoxymethoxy)ethyl, 4-(2-ethoxyethoxy)butyl, 4-(2-methoxyethoxy)butyl, 2-(methoxymethoxy)ethyl, and the like.

30

The term "alkoxyalkoxyimino," as used herein, refers to an alkoxyalkoxy group, as defined herein, appended to the parent molecular moiety through an imino group, as defined herein. Representative examples of alkoxyalkoxyimino include, but are not limited to, tert-butoxymethoxyimino, 2-(ethoxy)ethoxyimino, (2-methoxy)ethoxyimino, methoxymethoxyimino, and the like.

35

The term "alkoxyalkyl," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

40 Representative examples of alkoxyalkyl include, but are not limited to, tert-butoxymethyl, 2-ethoxyethyl, 2-methoxyethyl, methoxymethyl, and the like.

45 The term "alkoxyalkynyl," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkynyl group, as defined herein. Representative examples of alkoxyalkynyl include, but are not limited to, 3-(methoxy)propyn-1-yl, 4-(ethoxy)butyn-1-yl, and the like.

50

5

10

The term "alkoxyalkylcarbonyl," as used herein, refers to an alkoxyalkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkoxyalkylcarbonyl include, but are not limited to, 2-(ethoxy)ethylcarbonyl, 2-(methoxy)ethylcarbonyl, and the like.

15

5 The term "alkoxycarbonyl," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkoxycarbonyl include, but are not limited to, tert-butoxycarbonyl, ethoxycarbonyl, methoxycarbonyl, and the like.

20

10 The term "alkoxycarbonylalkenyl," as used herein, refers to one or two alkoxycarbonyl groups, as defined herein, appended to the parent molecular moiety through an alkenyl group, as defined herein. Representative examples of alkoxycarbonylalkenyl include, but are not limited to, 3-(methoxycarbonyl)propen-1-yl, , 4-(ethoxycarbonyl)buten-2-yl, 4-bis(ethoxycarbonyl)buten-2-yl, and the like.

25

15 The term "alkoxycarbonylalkoxy" as used herein refers to an alkoxycarbonyl group, as defined herein, appended to the parent molecular moiety through an alkoxy group. Representative examples of alkoxycarbonylalkoxy include methoxycarbonylmethoxy, ethoxycarbonylmethoxy, 2-(methoxycarbonyl)ethoxy, and the like.

30

20 The term "alkoxycarbonylalkoxyimino," as used herein refers to an alkoxycarbonylalkoxy group, as defined herein, appended to the parent molecular moiety through an imino group. Representative examples of alkoxycarbonylalkoxyimino include ethoxycarbonylmethoxyimino, 2-(methoxycarbonyl)ethoxyimino, and the like.

35

25 The term "alkoxycarbonylalkoxyiminoalkyl," as used herein refers to an alkoxycarbonylalkoxyimino group, as defined herein, appended to the parent molecular moiety through an alkyl group. Representative examples of alkoxycarbonylalkoxyiminoalkyl include 2-(ethoxycarbonylmethoxyimino)ethyl, 2-[2-(methoxycarbonyl)ethoxyimino]ethyl, and the like.

40

45 The term "alkoxycarbonylalkyl," as used herein, refers to an alkoxycarbonyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as

50

5

defined herein. Representative examples of alkoxy carbonyl alkyl include, but are not limited to, 3-(methoxycarbonyl)propyl, , 4-(ethoxycarbonyl)butyl, and the like.

10

The term "alkoxyimino," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through an imino group, as defined herein. Representative examples of alkoxyimino include, but are not limited to, ethoxyimino, methoxyimino, propoxyimino, isopropoxyimino, and the like.

15

The term "alkoxyiminoalkyl," as used herein, refers to an alkoxyimino group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyiminoalkyl include, but are not limited to, 2-(ethoxyimino)ethyl, 2-(methoxyimino)ethyl, 2-(propoxyimino)ethyl, 2-(isopropoxyimino)ethyl, and the like.

20

The term "alkyl," as used herein, refers to a straight or branched chain hydrocarbon containing from 1 to 6 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, and the like.

25

The term "alkylene," denotes a divalent group derived from a straight or branched chain hydrocarbon of from 1 to 3 carbon atoms. Representative examples of alkylene include, -CH₂- , -CH₂CH₂- , and -CH₂CH₂CH₂- .

30

The term "alkylcarbonyl," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkylcarbonyl include, but are not limited to, methylcarbonyl (acetyl), ethylcarbonyl, and the like.

40

The term "alkylcarbonyloxy," as used herein, refers to an alkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an oxy group, as defined herein. Representative examples of alkylcarbonyloxy include, but are not limited to, methylcarbonyloxy, ethylcarbonyloxy, and the like.

45

The term "alkylcarbonyloxyalkoxy," as used herein, refers to an alkylcarbonyloxy group, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of alkylcarbonyloxyalkoxy include, but are not limited to, 2-(methylcarbonyloxy)ethoxy, 3-(ethylcarbonyloxy)propoxy, and the like.

50

5

The term "alkylcarbonyloxyalkyl," as used herein, refers to an alkylcarbonyloxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkylcarbonyloxyalkyl include, but are not limited, 2-(methylcarbonyloxy)ethyl, 3-(ethylcarbonyloxy)propyl, and the like.

10

5 The term "alkylcarbonyloxyalkylthio," as used herein, refers to an alkylcarbonyloxyalkyl group, as defined herein, appended to the parent molecular moiety through a thio moiety, as defined herein. Representative examples of alkylcarbonyloxyalkylthio include, but are not limited, 2-(methylcarbonyloxy)ethylsulfanyl, 3-(ethylcarbonyloxy)propylsulfonyl, and the like.

15

10 The term "alkylsulfonyl," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of alkylsulfonyl include, but are not limited, methylsulfonyl, ethylsulfonyl, and the like.

20

25 The term "alkylthio," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a thio moiety, as defined herein. Representative examples of alkylthio include, but are not limited, methylsulfanyl, ethylsulfanyl, tert-butylsulfanyl, hexylsulfanyl, and the like.

30

30 The term "alkylthioalkyl," as used herein, refers to an alkylthio group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkylthioalkyl include, but are not limited, methylsulfanylmethyl, 2-(ethylsulfanyl)ethyl, and the like.

35

40 The term "alkynyl," as used herein, refers to a straight or branched chain hydrocarbon group containing from 2 to 6 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, 1-butynyl and the like.

45

45 The term "amino," refers to an -NZ₁Z₂ group wherein Z₁ and Z₂ are appended to the parent molecular moiety through a nitrogen atom. Z₁ and Z₂ are independently selected from hydrogen, alkyl, alkylcarbonyl, benzyl, cycloalkyl, cycloalkylalkyl, formyl, and phenyl. Representative examples of -NZ₁Z₂ include, but are not limited to, amino,

50

5

benzylamino, methylamino, acetylarnino, acetylmethylnino, cyclopropylarnino, cyclopropylmethylnino, dimethylarnino, phenylarnino, and the like.

10

The term "aminoalkyl," as used herein, refers to an amino group, as defined herein, appended to the parent molecular moiety through an alkyl moiety, as defined herein.

5 Representative examples of aminoalkyl include, but are not limited, 3-aminopropyl, 4-dimethylaminobutyl, and the like.

15

The term "aminoalkylcarbonyl," as used herein, refers to an aminoalkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl moiety, as defined herein. Representative examples of aminoalkylcarbonyl include, but are not

20

10 limited, 3-(amino)propylcarbonyl, 4-(dimethylarnino)butylcarbonyl, and the like.

The term "aminoalkynyl," as used herein, refers to an amino group, as defined herein, appended to the parent molecular moiety through an alkynyl moiety, as defined herein. Representative examples of aminoalkynyl include, but are not limited, 3-(amino)propyn-1-yl, 4-(dimethylarnino)butyn-1-yl, and the like.

25

15 The term "amino-protecting group" or "N-protecting group," refers to groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used nitrogen-protecting groups are disclosed in Greene, T. W., & Wuts, P. G. M. (1991). Protective Groups In Organic Synthesis (2nd ed.). New York: John Wiley & Sons. Preferred nitrogen-protecting groups are formyl, acetyl, benzoyl, 20 pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

35

30 The term "aminosulfonyl," as used herein, refers to an amino group, as defined herein, appended to the parent molecular moiety through a sulfonyl moiety, as defined herein. Representative examples of aminosulfonyl include, but are not limited, 40 aminosulfonyl, dimethylaminosulfonyl, diethylaminosulfonyl, and the like.

25

45 The term "aryl," as used herein, refers to a monocyclic-ring system, or a bicyclic-fused ring system wherein one or both of the fused rings are aromatic. Representative examples of aryl include, but are not limited to, azulenyl, indanyl, indenyl, naphthyl, phenyl, tetrahydronaphthyl, and the like.

50

5

10

15

20

25

30

35

40

45

50

55

The aryl groups of this invention can be substituted with 1, 2, or 3 substituents independently selected from alkenyl, alkenyloxy, alkennyloxyimino, alkenyloxyiminoalkyl, alkoxy, alkoxyalkoxy, alkoxyalkoxyalkyl, alkoxyalkoxyimino, alkoxyalkyl, alkoxyalkynyl, alcoxycarbonyl, aloxycarbonylalkenyl, aloxycarbonylalkyl, 5 alkoxy carbonylalkoxyimino, alkoxy carbonylalkoxyiminoalkyl, alkoxyimino, alkoxyiminoalkyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonyloxyalkoxy, alkylcarbonyloxyalkyl, alkylcarbonyloxyalkyl, alkylcarbonyloxyalkylthio, alkylsulfonyl, alkylthio, alkylthioalkyl, aminoalkynyl, aminosulfonyl, azido, carboxy, carboxyalkyl, cyano, cyanoalkyl, cycloalkyl, cycloalkylalkoxy, cycloalkylalkyl, cycloalkyloxy, cycloalkyloxyimino, 10 ethylenedioxy, formyl, formylalkyl, haloalkyl, haloalkylcarbonyl, halogen, hydroxy, hydroxyalkoxy, hydroxyalkoxyalkyl, hydroxyalkyl, hydroxyimino, hydroxyiminoalkyl, methylenedioxy, methylenyl, nitro, oxo, 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, 1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-4-one, phosphonato, spirocycle, (spirocycle)spirocycle, thioureylene, ureylene, -NZ₁₂Z₁₃, (NZ₁₂Z₁₃)alkyl, 15 (NZ₁₂Z₁₃)carbonyl, and (NZ₁₂Z₁₃)carbonyloxy wherein Z₁₂ and Z₁₃ are independently selected from hydrogen, alkoxyalkyl, alkyl, alkylcarbonyl, alkylsulfonyl, aminoalkylcarbonyl, aminosulfonyl, aryl, arylalkyl, arylalkylcarbonyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, formyl, haloalkylcarbonyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, heterocyclesulfonyl, and (NZ₁₄Z₁₅)alkyl wherein Z₁₄ and Z₁₅ are 20 independently selected from the group consisting of hydrogen, alkoxyalkoxyalkyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkyl, alkylcarbonyl, formyl, heterocycle, and hydroxyalkoxyalkyl.

The term "arylalkoxy," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein.

25 Representative examples of arylalkoxy include, but are not limited to, 2-phenylethoxy, 3-naphth-2-ylpropoxy, 5-phenylpentyloxy, and the like.

The term "arylalkoxycarbonyl," as used herein, refers to an arylalkoxy group, as 45 defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of arylalkoxycarbonyl include, but are not limited to, benzyloxycarbonyl, naphth-2-ylmethoxycarbonyl, and the like.

5

10

The term "arylalkoxyimino," as used herein, refers to an arylalkoxy group, as defined herein, appended to the parent molecular moiety through an imino group, as defined herein. Representative examples of arylalkoxyimino include, but are not limited to, 2-phenylethoxyimino, 3-naphth-2-ylpropoxyimino, 5-phenylpentyloxyimino, and the like.

15

The term "arylalkyl," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, 2-naphth-2-ylethyl, and the like.

20

The term "(aryl)alkyl," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through another aryl group, as defined herein. Representative examples of (aryl)aryl include, but are not limited to, biphenyl, 4'-methoxybiphenyl, and the like.

25

The term "aryloxy," refers to an aryl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of aryloxy include, but are not limited to, phenoxy, naphthoxy, 4-chlorophenoxy, 4-methylphenoxy, 3,5-dimethoxyphenoxy, and the like.

30

The term "azido," as used herein, refers to a -N₃ group.

The term "carbonyl," as used herein, refers to a -C(O)- group.

The term "carboxy," as used herein, refers to a -CO₂H group.

35

The term "carboxyalkyl," as used herein, refers to a carboxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of carboxyalkyl include, but are not limited to, carboxymethyl, 2-carboxyethyl, 3-carboxypropyl, and the like.

40

The term "cyano," as used herein, refers to a -CN group.

The term "cyanoalkyl," as used herein, refers to a cyano group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

45

Representative examples of cyanoalkyl include, but are not limited to, cyanomethyl, 2-cyanoethyl, 3-cyanopropyl, and the like.

50

5

The term "cycloalkyl," as used herein, refers to a saturated cyclic hydrocarbon group containing from 3 to 8 carbons. Representative examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

10

The cycloalkyl groups of this invention can be substituted with 1 or 2 substituents

- 5 independently selected from alkenyl, alkenyloxy, alkenyloxyimino, alkenyloxyiminoalkyl, alkoxy, alkoxyalkoxy, alkoxyalkoxyalkyl, alkoxyalkoxyimino, alkoxyalkyl, alkoxyalkynyl, alkoxy carbonyl, alkoxy carbonylalkenyl, alkoxy carbonylalkyl, alkoxy carbonylalkoxyimino, alkoxy carbonylalkoxyiminoalkyl, alkoxyimino, alkoxyiminoalkyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonyloxyalkoxy, alkylcarbonyloxyalkyl, alkylcarbonyloxyalkylthio, alkylsulfonyl, alkylthio, alkylthioalkyl, aminoalkynyl, aminosulfonyl, azido, carboxy, carboxyalkyl, cyano, cyanoalkyl, cycloalkyl, cycloalkylalkoxy, cycloalkylalkyl, cycloalkyloxy, cycloalkyloxyimino, ethylenedioxy, formyl, formylalkyl, haloalkyl, haloalkylcarbonyl, halogen, hydroxy, hydroxyalkoxy, hydroxyalkoxyalkyl, hydroxyalkyl, hydroxyimino, hydroxyiminoalkyl, 15 methylenedioxy, methylenyl, nitro, oxo, 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, 1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-4-one, phosphonato, spirocycle, (spirocycle)spirocycle, thioureylene, ureylene, -NZ₁₂Z₁₃, (NZ₁₂Z₁₃)alkyl, (NZ₁₂Z₁₃)carbonyl, and (NZ₁₂Z₁₃)carbonyloxy wherein Z₁₂ and Z₁₃ are independently selected from hydrogen, alkoxyalkyl, alkyl, alkylcarbonyl, alkylsulfonyl, 20 aminoalkylcarbonyl, aminosulfonyl, aryl, arylalkyl, arylalkylcarbonyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, formyl, haloalkylcarbonyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, heterocyclesulfonyl, and (NZ₁₄Z₁₅)alkyl wherein Z₁₄ and Z₁₅ are independently selected from the group consisting of hydrogen, alkoxyalkoxyalkyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkyl, alkylcarbonyl, formyl, heterocycle, and 25 hydroxyalkoxyalkyl.

30

35

40

50

The term "cycloalkylalkoxy," as used herein, refers to cycloalkyl group, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of cycloalkylalkoxy include, but are not limited to, cyclopropylmethoxy, 2-cyclobutylethoxy, cyclopentylmethoxy, cyclohexylmethoxy, 4-cycloheptylbutoxy, and the like.

55

5

The term "cycloalkylalkyl," as used herein, refers to cycloalkyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of cycloalkylalkyl include, but are not limited to, cyclopropylmethyl, 2-cyclobutylethyl, cyclopentylmethyl, cyclohexylmethyl and 4-cycloheptylbutyl, and the like.

10

The term "cycloalkylcarbonyl," as used herein, refers to cycloalkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of cycloalkylcarbonyl include, but are not limited to, cyclopropylcarbonyl, 2-cyclobutylcarbonyl, cyclohexylcarbonyl, and the like.

15

The term "cycloalkyloxy," as used herein, refers to cycloalkyl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of cycloalkyloxy include, but are not limited to, cyclopropyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

20

25

The term "cycloalkyloxyimino," as used herein, refers to cycloalkyloxy group, as defined herein, appended to the parent molecular moiety through an imino group, as defined herein. Representative examples of cycloalkyloxyimino include, but are not limited to, cyclopropyloxyimino, cyclopentyloxyimino, cyclohexyloxyimino, and the like.

30

The term "ethylenedioxy," as used herein, refers to a -OCH(R₂₀)CH(R₂₁)O- group wherein the oxygen atoms of the ethylenedioxy group are attached to the parent molecular moiety through one carbon atom forming a 5 membered ring or the oxygen atoms of the ethylenedioxy group are attached to the parent molecular moiety through two adjacent carbon atoms forming a six membered ring. R₂₀ and R₂₁, are independently selected from hydrogen and alkyl or R₂₀ and R₂₁ together with the carbon atoms to which they are attached can join to form a 5 or 6 membered ring optionally containing 1 heteroatom selected from NH, O, or S. Representative examples of ethylenedioxy include, but are not limited to, 3,5-dimethyl-1,2-cyclopentanediol, tetrahydro-3,4-furandiol, 1,2-cyclopentanediol, and the like.

40

45

The term "formyl," as used herein, refers to a -C(O)H group.

50

The term "formylalkyl," as used herein, refers to a formyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

55

5

Representative examples of formylalkyl include, but are not limited to, formylmethyl, 2-formylethyl, and the like.

10

The term "halo" or "halogen," as used herein, refers to -Cl, -Br, -I or -F.

15

The term "haloalkoxy," as used herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of haloalkoxy include, but are not limited to, chloromethoxy, 2-fluoroethoxy, trifluoromethoxy, pentafluoroethoxy, and the like.

20

The term "haloalkyl," as used herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, 2-chloro-3-fluoropentyl, and the like.

25

The term "haloalkylcarbonyl," as used herein, refers to a haloalkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of haloalkylcarbonyl include, but are not limited to, 2-fluoroethylcarbonyl, trifluoromethylcarbonyl, pentafluoroethylcarbonyl, and the like.

30

The term "heterocycle" as used herein, refers to a monocyclic, bicyclic, or tricyclic ring system. Monocyclic ring systems are exemplified by any 3- or 4-membered ring containing a heteroatom independently selected from oxygen, nitrogen and sulfur; or a 5-, 6- or 7-membered ring containing one, two or three heteroatoms wherein the heteroatoms are independently selected from nitrogen, oxygen and sulfur. The 5-membered ring has from 0-2 double bonds and the 6- and 7-membered ring have from 0-3 double bonds.

35

Representative examples of monocyclic ring systems include, but are not limited to, azetidinyl, azepinyl, aziridinyl, diazepinyl, 1,3-dioxolanyl, dioxanyl, dithianyl, furyl, imidazolyl, imidazolinyl, imidazolidinyl, isothiazolyl, isothiazolinyl, isothiazolidinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxadiazolyl, oxadiazolinyl, oxadiazolidinyl, oxazolyl, oxazolinyl, oxazolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, pyridyl, pyrimidinyl, pyridazinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, thiadiazolyl, thiadiazolinyl, thiadiazolidinyl, thiazolyl, thiazolinyl, thiazolidinyl, thiophenyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl, thiopyranyl, triazinyl, triazolyl,

40

45

50

5

trithianyl, and the like. Bicyclic ring systems are exemplified by any of the above monocyclic ring systems fused to an aryl group as defined herein, a cycloalkyl group as defined herein, or another monocyclic ring system. Bicyclic ring systems are further exemplified by any of the above monocyclic ring systems containing an alkylene of 1-3

10

carbon atoms attached to two non-adjacent carbon atoms of the monocyclic ring system. Representative examples of bicyclic ring systems include but are not limited to, for

15

example, benzimidazolyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzodioxinyl, 1,3-benzodioxolyl, cinnolinyl, hexahydro-1H-furo[3,4-c]pyrrolyl, indazolyl, indolyl, indolinyl, indolizinyl,

20

naphthyridinyl, isobenzofuranyl, isobenzothiophenyl, isoindolyl, isoindolinyl, isoquinolyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1,3-dioxa-8-

25

azaspiro[4.5]decanyl, 1,5-dioxa-9-azaspiro[5.5]undecanyl, 1-oxa-4-thia-8-azaspiro[4.5]decanyl, 1-oxa-4,4-dioxa-4-thia-8-azaspiro[4.5]decanyl, 1-oxa-4-oxo-4-thia-

30

8-azaspiro[4.5]decanyl, phthalazinyl, pyranopyridyl, 2,4-(1H,3H)-quinazolinedion-3-yl, quinolyl, quinolizinyl, quinoxalinyl, quinazolinyl, (3aR,6aS)-tetrahydro-3aH-

35

[1,3]dioxolo[4,5-c]pyrrol-2-one, tetrahydroisoquinolyl, tetrahydroquinolyl, thiopyranopyridyl, and the like. Tricyclic rings systems are exemplified by any of the

above bicyclic ring systems fused to an aryl group as defined herein, a cycloalkyl group as defined herein, or a monocyclic ring system. Representative examples of tricyclic ring

systems include, but are not limited to, acridinyl, carbazolyl, carbolinyl, dibenzofuranyl,

40

2,4(1H,3H)-quinazolinedione, dibenzothiophenyl, 4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl, naphthofuranyl, naphthothiophenyl, oxanthrenyl, phenazinyl,

45

phenoxathiinyl, phenoxazinyl, phenothiazinyl, thianthrenyl, thioxanthenyl, xanthenyl, and the like.

40 25 The heterocycles of this invention can be substituted with 1, 2, or 3 substituents

independently selected from alkenyl, alkenyloxy, alkenyloxyimino, alkenyloxyiminoalkyl, alkoxy, alkoxyalkoxy, alkoxyalkoxyalkyl, alkoxyalkoxyimino, alkoxyalkyl,

45

alkoxyalkynyl, alcoxycarbonyl, alcoxycarbonylalkenyl, alcoxycarbonylalkyl,

alkoxycarbonylalkoxyimino, aloxycarbonylalkoxyiminoalkyl, alkoxyimino,

30 alkoxyiminoalkyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonyloxyalkoxy,

50

5

alkylcarbonyloxyalkyl, alkylcarbonyloxyalkylthio, alkylsulfonyl, alkylthio, alkylthioalkyl, aminoalkynyl, aminosulfonyl, azido, carboxy, carboxyalkyl, cyano, cyanoalkyl, cycloalkyl, cycloalkylalkoxy, cycloalkylalkyl, cycloalkyloxy, cycloalkyloxyimino, ethylenedioxy, formyl, formylalkyl, haloalkyl, haloalkylcarbonyl, halogen, hydroxy,

10

hydroxyalkoxy, hydroxyalkoxyalkyl, hydroxyalkyl, hydroxyimino, hydroxyiminoalkyl, methylenedioxy, methylenyl, nitro, oxo, phosphonato, spirocycle, (spirocycle)spirocycle, thioureylene, ureylene, - $NZ_{12}Z_{13}$, ($NZ_{12}Z_{13}$)alkyl, ($NZ_{12}Z_{13}$)carbonyl, and

15

($NZ_{12}Z_{13}$)carbonyloxy wherein Z_{12} and Z_{13} are independently selected from hydrogen, alkoxyalkyl, alkyl, alkylcarbonyl, alkylsulfonyl, aminoalkylcarbonyl, aminosulfonyl, aryl,

20

arylalkyl, arylalkylcarbonyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, formyl, haloalkylcarbonyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, heterocyclesulfonyl, and ($NZ_{14}Z_{15}$)alkyl wherein Z_{14} and Z_{15} are independently selected

25

from the group consisting of hydrogen, alkoxyalkoxyalkyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkyl, alkylcarbonyl, formyl, heterocycle, and hydroxyalkoxyalkyl.

15 Representative examples include, but are not limited to 4,4-(*cis*-1,2-dioxycyclopentyl)piperidinyl,

30

The term "heterocyclealkoxy," as used herein, refers to a heterocycle group, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of heterocyclealkoxy include, but are not limited

20 to, 2-pyrid-3-ylethoxy, 3-quinolin-3-ylpropoxy, 5-pyrid-4-ylpentyl, and the like.

35

The term "heterocyclealkoxyimino," as used herein, refers to a heterocyclealkoxy group, as defined herein, appended to the parent molecular moiety through an imino group, as defined herein. Representative examples of heterocyclealkoxyimino include, but are not limited to, 2-pyrid-3-ylethoxyimino, 3-quinolin-3-ylpropoxyimino, 5-pyrid-4-

40

25 ylpentyloxyimino, 3-(4-morpholinyl)propoxyimino, and the like.

50

The term "heterocyclealkyl," as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

45

Representative examples of heterocyclealkyl include, but are not limited to, pyrid-3-ylmethyl, 2-pyrimidin-2-ylpropyl, and the like.

55

5

10

The term "heterocyclealkylcarbonyl," as used herein, refers to a heterocyclealkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of heterocyclealkylcarbonyl include, but are not limited to, pyrid-3-ylmethylcarbonyl, 3-pyrimidin-2-ylpropylcarbonyl, and the like.

15

The term "(heterocycle)aryl," as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety a aryl group, as defined herein. Representative examples of (heterocycle)aryl include, but are not limited to, 4-(pyridin-3-yl)phenyl, 4-(pyrimidin-2-yl)phenyl, and the like.

20

The term "heterocyclecarbonyl," as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of heterocyclecarbonyl include, but are not limited to, pyrid-3-ylcarbonyl, quinolin-3-ylcarbonyl, and the like.

25

The term "heterocycleimino," as used herein, refers to a heterocycle group, as defined herein, appended to the parent molecular moiety through an imino group, as defined herein. Representative examples of heterocycleimino include, but are not limited to, 4-morpholinylimino, and the like.

30

The term "heterocycloxy," as used herein, refers to a heterocycle group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of heterocycloxy include, but are not limited to, pyrid-3-yloxy, quinolin-3-yloxy, and the like.

35

The term "heterocycloxyalkyl," as used herein, refers to a heterocycloxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of heterocycloxyalkyl include, but are not limited to, pyrid-3-yloxymethyl, 2-quinolin-3-yloxyethyl, and the like.

40

45

The term "heterocycloxyimino," as used herein, refers to a heterocycloxy group, as defined herein, appended to the parent molecular moiety through an imino group, as defined herein. Representative examples of heterocycloxyimino include, but are not limited to, pyrid-3-yloxyimino, quinolin-3-yloxyimino, and the like.

50

55

5

The term "heterocycloxyiminoalkyl," as used herein, refers to a heterocycloxyimino group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of heterocycloxyiminoalkyl include, but are not limited to, 2-(pyrid-3-yloxyimino)ethyl, 2-(quinolin-3-yloxyimino)ethyl, and the like.

10

The term "heterocyclesulfonyl," as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of heterocyclesulfonyl include, but are not limited to, pyrid-3-ylsulfonyl, quinolin-3-ylsulfonyl, 4-morpholinylsulfonyl, and the like.

15

10 The term "hydroxy," as used herein, refers to an -OH group.

20

The term "hydroxyalkoxy," as used herein, refers to one or two hydroxy groups, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of hydroxyalkoxy include, but are not limited to, 2-hydroxyethoxy, 2,3-dihydroxypropoxy, 4-hydroxybutoxy, and the like.

25

15 The term "hydroxyalkoxyalkyl," as used herein, refers to a hydroxyalkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyalkoxyalkyl include, but are not limited to, 2-[2-(hydroxy)ethoxy]ethyl, 2-[3-(hydroxy)propoxy]ethyl, 4-hydroxybutoxymethyl, and the like.

30

20 The term "hydroxyalkyl," as used herein, refers to one or two hydroxy groups, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyalkyl include, but are not limited to, 2-hydroxyethyl, 2,3-dihydroxypropyl, and the like.

35

25 The term "hydroxyimino," as used herein, refers to a HON= group.

40

25 The term "hydroxyiminoalkyl," as used herein, refers to a hydroxyimino group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyiminoalkyl include, but are not limited to, 2-(hydroxyimino)ethyl, 3-(hydroxyimino)propyl, and the like.

45

30 The term "imino," as used herein, refers to a HN= group.

50

30 The term "mammal," has its ordinary meaning and includes human beings.

55

5

10

The term "methylenedioxy," as used herein, refers to a -OCH₂O- group wherein the oxygen atoms of the methylenedioxy are attached to the parent molecular moiety through two adjacent carbon atoms forming a 5 membered ring. The carbon atom of methylenedioxy group is optionally substituted with one substituent selected from alkyl and oxo.

15

The term "methylene," as used herein refers to a H₂C= group.

20

The term "nitro," as used herein, refers to a -NO₂ group.

25

The term "oxo," as used herein, refers to a O= moiety.

The term "oxy," as used herein, refers to a -O- moiety.

10

The term "phosphonato," refers to a (R₉₃O)₂P(O)O- group wherein R₉₃ is alkyl.

20

The term "spirocycle," as used herein, refers to a -X₁(CH₂)_pX₂- group wherein X₁ and X₂ are independently selected from CH₂, NH, O, S, S(O), and S(O)₂; and p is an integer from 2-3. X₁ and X₂ are attached to the parent molecular moiety through one carbon atom forming a 5 or 6 membered ring. Representative examples of spirocycle

25

include, but are not limited to 1,3-dioxolane, 1,3-dioxane, 1,3-oxathiane, 1,3-oxazinane, and the like.

30

The spirocycles of this invention are optionally substituted with 1, 2, or 3 substituents independently selected from alkoxy, alkoxyalkyl, alkoxy carbonyl, alkyl, alkyl carbonyl, aminocarbonyl, benzyloxycarbonyl, and formyl. The substituents can be attached to nitrogen or any of the carbon atoms.

35

The term "(spirocycle)spirocycle," as used herein, refers to a spirocycle, as defined herein, attached to the parent molecular moiety through a spirocycle, as defined herein. Representative examples of spirocycle-spirocycles include, but are not limited to, 1,7,9-trioxaspiro[4.5]decane, 1,4,7,9-tetraoxaspiro[4.5]decane, and the like.

40

The term "thio," as used herein, refers to a -S- moiety.

45

The term "thioureylene," as used herein, refers to -NR₉₅C(S)NR₉₆R₉₉, wherein R₉₅, R₉₆, and R₉₉ are independently selected from hydrogen, alkyl, aryl, and arylalkyl, as defined herein.

50

5

The term "ureylene," as used herein, refers to $-NR_{97}C(O)NR_{98}R_{99}$, wherein R_{97} , R_{98} , and R_{99} are independently selected from hydrogen, alkyl, aryl, and arylalkyl, as defined herein.

10

In a further aspect of the present invention pharmaceutical compositions are disclosed which comprise a compound of the present invention in combination with a pharmaceutically acceptable carrier.

15

The present invention includes one or more compounds, as set forth above, formulated into compositions together with one or more non-toxic physiologically tolerable or acceptable diluents, carriers, adjuvants or vehicles that are collectively

20

referred to herein as diluents, for parenteral injection, for oral administration in solid or liquid form, for rectal or topical administration, or the like. As is well known in the art, a compound of the present invention can exist in a variety of forms including pharmaceutically-acceptable salts, amides and the like.

25

Compositions may be prepared that will deliver the correct amount of a compound or compounds of the invention. The following dosages are thought to provide the optimal therapy: iv infusions: 0.1- 250 nmol/kg/minute, preferably from 1-50 nmol/kg/minute; oral: 0.01-250 μ Mol/kg/day, preferably from about 0.1-50 μ Mol/kg/day; these oral molar dosage ranges correspond to 0.005-125 mg/kg/day, preferably 0.05-25 mg/kg/day. For treatment of acute disorders the preferred route of administration is intravenous; the preferred method of treating chronic disorders is orally by means of a tablet or sustained release formulation.

30

"Pharmaceutically-acceptable amide" refers to the pharmaceutically-acceptable, nontoxic amides of the compounds of the present invention which include amides formed with suitable organic acids or with amino acids, including short peptides consisting of from 1-to-6 amino acids joined by amide linkages which may be branched or linear, wherein the amino acids are selected independently from naturally-occurring amino acids, such as for example, glycine, alanine, leucine, valine, phenylalanine, proline, methionine, tryptophan, asparagine, aspartic acid, glutamic acid, glutamine, serine, threonine, lysine, arginine, tyrosine, histidine, ornithine, and the like.

50

5

"Pharmaceutically acceptable salts" refers to the pharmaceutically-acceptable, nontoxic, inorganic or organic acid addition salts of the compounds of the present invention, as described in greater detail below.

10

Compounds of the present invention can exist as stereoisomers wherein

- 5 asymmetric or chiral centers are present. These compounds are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom.

15

The present invention contemplates various stereoisomers and mixtures thereof.

Stereoisomers include enantiomers and diastereomers. Individual stereoisomers of compounds of the present invention can be prepared synthetically from commercially

20

available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

30

The compounds of the present invention can be used in the form of pharmaceutically-acceptable salts derived from inorganic or organic acids. These salts include, but are not limited to, the following: acetate, adipate, alginate, aspartate,

20 benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, flavianate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, 35 persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate.

40

Appropriate cationic salts are also readily prepared by conventional procedures such as treating an acid of Formula I with an appropriate amount of base, such as an alkali or alkaline earth metal hydroxide, e.g., sodium, potassium, lithium, calcium, or 45 magnesium, or an organic base such as an amine, e.g., dibenzylethylenediamine, 30

50

5

cyclohexylamine, dicyclohexylamine, triethylamine, piperidine, pyrrolidine, benzylamine, and the like, or a quaternary ammonium hydroxide such as tetramethylammonium hydroxide and the like. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dialkyl sulfates; long chain halides such as decyl, lauryl, myristyl, and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

10

5 The salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional methods, such as by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt forming inorganic acid or base in a suitable solvent or various combinations of solvents.

15

10 20 Further included within the scope of the present invention are pharmaceutical compositions comprising one or more of the compounds of formula I prepared and formulated in combination with one or more non-toxic pharmaceutically acceptable carriers compositions, in the manner described below.

25

30 Compositions suitable for parenteral injection may comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions.

35

20 Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

40

45 50 These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Prevention of the action of microorganisms may be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride and the like. Prolonged absorption

55

5

of the injectable pharmaceutical form may be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

10

If desired, and for more effective distribution, the compounds may be incorporated into slow-release or targeted-delivery systems, such as polymer matrices, liposomes, and microspheres. They may be sterilized, for example, by filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions, which may be dissolved in sterile water, or some other sterile injectable medium immediately before use.

15

Solid dosage forms for oral administration may include capsules, tablets, pills,

20

powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier), such as sodium citrate or dicalcium phosphate, and additionally (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol and silicic acid; (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; (c)

25

humectants, as for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates and sodium carbonate; (e) solution retarders, as for example paraffin; (f) absorption

30

accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin

and bentonite; and I lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate or mixtures thereof. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

35

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules, using such excipients as lactose or milk sugar, as well as high molecular weight polyethylene glycols, and the like.

40

Solid dosage forms such as tablets, dragees, capsules, pills and granules may be prepared with coatings and shells, such as enteric coatings and others well known in this art. They may contain pacifying agents, and may also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a

50

5

delayed manner. Examples of embedding compositions which may be used are polymeric substances and waxes.

10

The active compounds may also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

15

5 Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

20

10 Besides such inert diluents, these liquid dosage forms may also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

25

15 Susensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

30

20 Compositions for rectal or vaginal administrations are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

35

25 Dosage forms for topical or transdermal administration of a compound of this invention further include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or transdermal patches. Transdermal administration via a transdermal patch is a particularly effective and preferred dosage form of the present invention. The active component is admixed under sterile conditions with a pharmaceutically acceptable

40

5

10

15

carrier and any needed preservative, buffers or propellants as may be required. It is known that some agents may require special handling in the preparation of transdermal patch formulations. For example, compounds that are volatile in nature may require admixture with special formulating agents or with special packaging materials to assure proper dosage delivery. In addition, compounds which are very rapidly absorbed through the skin may require formulation with absorption-retarding agents or barriers. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

20

25

30

The present compounds may also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes may be used. The present compositions in liposome form may contain, in addition to the compounds of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N. Y., (1976), p 33 et seq.

20

Synthetic Methods

35

40

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the invention may be prepared. The R groups are as defined above unless otherwise noted below.

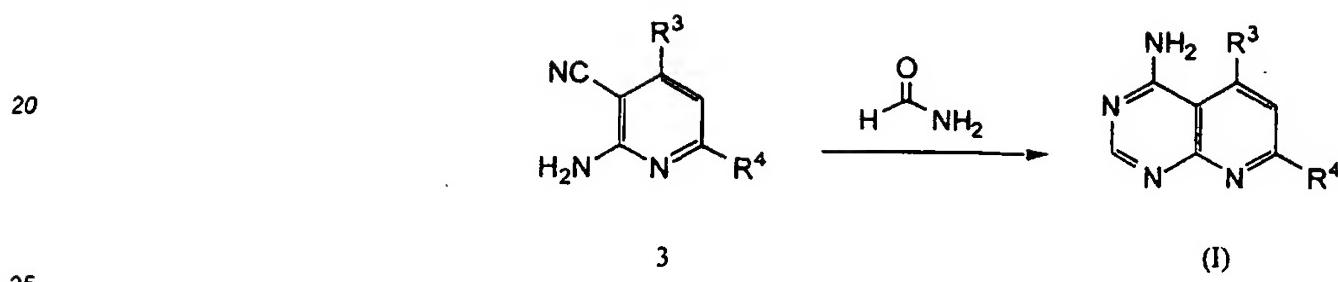
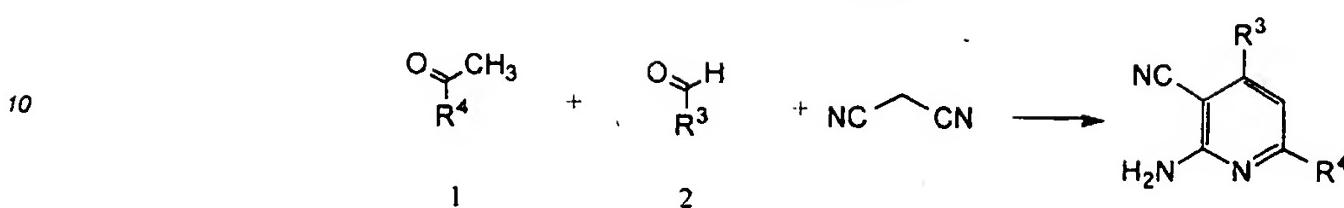
25

45

50

55

5

Scheme 1

The compounds of the present invention may be synthesized by methods illustrated

- 5 in Schemes 1 and 2. In accordance with Scheme 1, the 5,7-disubstituted compounds
 30 wherein R⁴ and R³ are aryl or a heterocyclic group may be prepared by a modification of a
 method of Kambe et al., *Synthesis*, 1980, 366-368. An appropriately substituted
 acetophenone (1, the "R⁴ Reagent"), wherein R⁴ is aryl or a heterocyclic group, an
 appropriately substituted aldehyde (2, the "R³ Reagent"), R³ is aryl or a heterocyclic group,
 35 and malononitrile are heated in the presence of ammonium acetate, or another suitable
 ammonium salt, such as for example, ammonium propionate, ammonium iodide, or the
 like, in an aprotic solvent to produce compound (3). The water of the reaction may
 40 be removed by use of a Dean Stark apparatus or by another suitable means, such as 4 Å
 molecular sieves. Suitable aprotic solvents include benzene, toluene, methylene chloride,
 45 DMF, THF, dioxane, and the like. The reaction may be performed at from about 40 °C to
 about 200 °C, and preferably at the reflux temperature of the solvent, for from about 1
 hour to about 24 hours, preferably about 4 hours to 8 hours. The product (3) is preferably
 purified by chromatography after isolation from the reaction mixture. The above reaction
 may also proceed by contacting the aldehyde (2) with malononitrile and isolating the

50

5

resulting dicyano R³ substituted alkene which is then reacted with the ketone (1) to form, upon addition of ammonium and cyclization, compound (3). Aliphatic aldehydes do not work effectively by this route. The ketone (1) may, however, include R⁴ as alkyl groups.

10

The acetophenone starting materials (1) may be obtained commercially, or

5 prepared easily by Friedel-Craft acylation of a suitable aromatic substrate, for example.

15

The appropriate aldehyde starting materials (2) also may be obtained commercially, or may be prepared easily, for example by reductions of esters or acids with DIBAL or another suitable hydride reducing agent, or oxidation of alcohols under Swern conditions, for example.

20

10 Compound (3) is then treated with excess formamide by heating at reflux. The formation of product is monitored by TLC, and when the reaction is complete (after about 1 to about 8 hours) the reaction mixture is cooled to room temperature. The 5,7-disubstituted pyrido[2,3-d]pyrimidine product I is then removed by filtration and purified by column chromatography. This compound may then be partially or fully reduced by 15 catalytic hydrogenation to the partially saturated or fully saturated version(s) (on the right side of the molecule) of the compounds shown in Scheme I or of Formula I. Stereoisomers produced during these reduction steps are included within the scope of the invention. The present invention also contemplates reductions which produce single bonds between the 5,6 and 7,8 positions and a double bond between the 6,7 carbons. The 20 stereoisomers may be isolated and purified by conventional means.

30

In accordance with Scheme 2 are prepared compounds of Formula I wherein R⁴ is preferably an aryl, heterocycle or heterocyclic group, and R³ is loweralkyl, loweralkenyl, loweralkynyl, or an arylalkyl group. In addition, R⁴ may be selected from those additional groups listed in R³.

35

25 Compound (4, the "R³ Reagent") may be obtained commercially or prepared from the precursor ester (5) or alcohol (5) by suitable reactions. Compound (5) may be reduced with a suitable reducing agent, such as for example, diisobutylaluminum hydride or another similar alkylaluminum hydride, under conditions well known to the art. Compound (6) may be oxidized to the aldehyde (4) Swern oxidation conditions, or other

50

5

reactions known to those skilled in the art. The desired compound (4) is freshly prepared before its use in the reaction described below.

10

Compound (9), the "R⁴ Reagent" may be prepared from the precursor alpha-bromo ketone (7) by a two-step procedure. Compound (7) is treated with triphenylphosphine in 5 the presence of a base, such as for example, triethyl amine, to give compound (8). Compound (8) is then treated with an alkali metal base, such as NaOH or the like, to give 15 compound (9). The procedure is normally accomplished by vigorous mixing of a solution of (8) in an organic solvent with an aqueous solution of base.

10

Compounds (4) and (9) are mixed and the mixture is held at ambient temperature 20 until the reaction is complete (monitoring by TLC), and the product (10) is purified by chromatography. A mixture of the cis and trans isomers is obtained and taken to the next step without further separation. Compound (10) is condensed with malononitrile by 25 heating in the presence of ammonium acetate as defined for Scheme 1 above to produce compound (11).

30

35

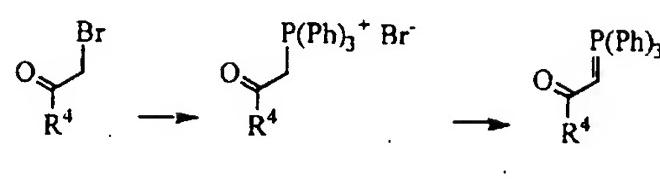
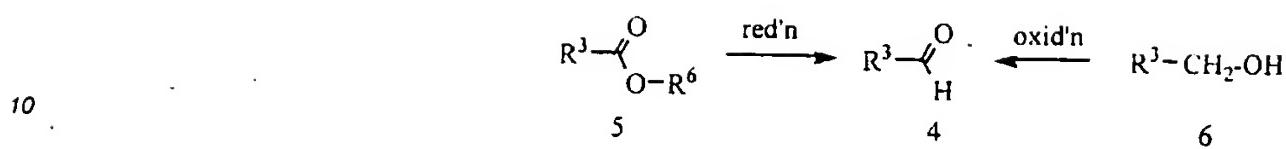
40

45

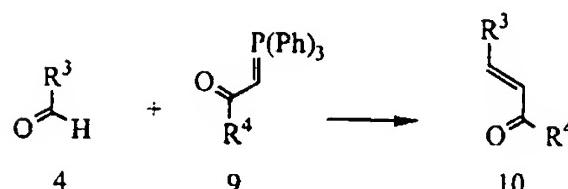
50

5

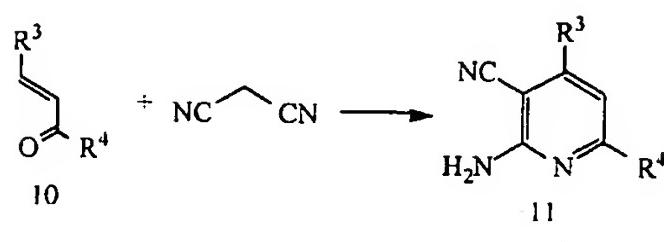
Scheme 2



20



30



35

40

45 5 formation of product is monitored by TLC, and when the reaction is complete (routinely, after about 1 to about 8 hours) the reaction mixture is cooled to room temperature. The 5,7-disubstituted pyrido[2,3-d]pyrimidine product I is then removed by filtration and purified by column chromatography. In an alternate procedure, compound (11) is treated by heating with formamidine acetate in ethoxycethanol, followed by purification by flash chromatography. In another alternate procedure, compound (11) and ammonium sulfate

10

50

5

10

5

15

20

25

30

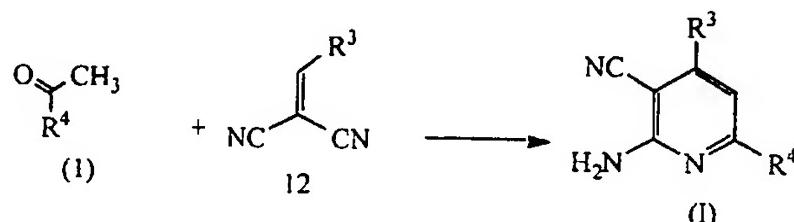
35

40

45

50

are heated at reflux in triethyl orthoformate for about 1 to about 8 hours, but preferably about 2 hours. The reaction mixture is cooled and added to a mixture of ammonia in ethanol. The mixture is stirred for about 12 to 24 hours at 25 °C, then at reflux for from one to 4 hours, and the solvent is removed in vacuo. The residue is purified by trituration with chloroform/ethyl acetate, and the product may be converted to a hydrochloride salt by suspension in 3M HCl, followed by lyophilization.

Scheme 3

Scheme 3 illustrates an alternate method for preparing the compounds I of the invention. Compounds (1), prepared as described above, are reacted with a dicyanoalkene compound (12) by heating with a suitable ammonium salt, such as for example, ammonium acetate, ammonium propionate, ammonium iodide, or the like, at reflux in an alcoholic or aprotic solvent to give the compound I. Suitable solvents for the reaction may be easily determined by those skilled in the art, without undue trial and error, and may include, for example, ethanol, propanol, isopropanol, t-butanol, n-butanol, 1,2-dichloroethane, benzene, chloroform, carbon tetrachloride, toluene, dioxane, dimethoxyethane, and the like. A preferred solvent is 1,2-dichloroethane. The dicyano compounds (12) may be prepared from the precursor aldehyde (4) by treatment with malononitrile in 1:1 H₂O:EtOH in the presence of a catalytic amount of glycine according to the method of Bastus (*Tetrahedron Lett.*, 1963: 955), or alternately MgO in dichloromethane or a similar aprotic solvent (cf. Broekhuis, et al., *Recl. J. R. Neth. Chem. Soc.*, **99**: 6-12 (1980); Moison, et al. *Tetrahedron* (1987), **43**:537-542).

To prepare compounds of formula I wherein R¹ and R² are not both hydrogen atoms, it is possible to prepare the desired derivative from the compound of Formula I wherein R¹ and R² are both hydrogen atoms. When R¹ or R² is loweralkyl this may be

5

accomplished by reaction of the free amino group with the appropriate alkylating reagent, such as an alkyl halide, an alkyl mesylate or an alkyl tosylate, for example, in the presence of a base such as triethylamine or potassium carbonate in a suitable solvent, such as for example, methylene chloride or THF. When R^1 or R^2 is arylalkyl this may be

10

5 accomplished by reaction of the free amino group with the appropriate arylalkyl halide, an alkyl mesylate or an alkyl tosylate, for example, in the presence of a base such as triethylamine or potassium carbonate in a suitable solvent, such as for example, methylene chloride or THF. When R¹ or R² is acyl this may be accomplished by reaction of the free amino group with the appropriate acid anhydride, acyl chloride or activated acyl group, in

16

10 the presence of a base such as triethylamine or potassium carbonate in a suitable solvent, such as for example, methylene chloride or THF. When R¹ and R² are taken together with the nitrogen atom to which they are attached to form a 5-to-7 membered ring optionally containing an additional oxygen or nitrogen atom, the compound may be prepared by reacting a precursor compound having a halogen atom in place of the amino group at the

20

15 4-position with a 5-7 membered ring compound optionally containing an additional oxygen or nitrogen atom. Examples of such compounds include, but are not limited to, morpholine, piperidine, pyrrolidine, piperazine, thiomorpholine, and the like. Also, this alternate procedure may be used to prepare alkyl substituted amino compounds, for

30

example by reacting the chloro compound with a mono- or disubstituted amine, such as
20 for example, diethylamine, allyl amine, dibutylamine. This reaction takes place readily in
a solvent such as methylene chloride, for example, in the presence of a tertiary amine. The
precursor compound having a halogen atom in place of the amino group at the 4-position
may be prepared by substitution of triethyl orthoformate for the formamide followed by
chlorination of the ring by treatment with phosphorous oxychloride or thionyl chloride in
25 the presence of DMF in Scheme 1 wherein compound (3) is converted to compound I.

Method of Inhibiting Kinase

45

In yet another aspect of the present invention a process of inhibiting adenosine kinase is disclosed. In accordance with that process, an adenosine kinase enzyme is exposed to an effective inhibiting amount of an adenosine kinase inhibitor compound of

50

55

5

the present invention. Means for determining an effective inhibiting amount are well known in the art.

10

The adenosine kinase to be inhibited can be located in vitro, in situ or in vivo. Where the adenosine kinase is located in vitro, adenosine kinase is contacted with the inhibitor compound, typically by adding the compound to an aqueous solution containing the enzyme, radiolabeled substrate adenosine, magnesium chloride and ATP. AK activity of cell supernatants was assayed radiometrically. Assays were carried out at ambient temperature in a final volume of 100 µL. The reaction mixture contained 64 mM Tris HCl (pH 7.5), 0.2 mM MgCl₂, 1 mM ATP, 0.2 µM U-[¹⁴C]-adenosine or [³H]-adenosine and appropriate volumes of rat brain cytosol as a source of adenosine kinase. The reaction was terminated after 15 min by spotting 40 µL of the reaction mixture onto disks of Whatman DE-81 anion exchange paper. DE-81 disks were then air-dried, washed for 10 minutes in 2 mM ammonium formate, then rinsed successively with distilled water, methanol and acetone, and dried. DE-81 disks were then soaked for 5 minutes in 0.1N HCl/0.4 M KCl before addition of scintillation cocktail and counting by liquid scintillation counting. The enzyme can exist in intact cells or in isolated subcellular fractions containing the enzyme. The enzyme is then maintained in the presence of the inhibitor for a period of time and under suitable physiological conditions. Means for determining maintenance times are well known in the art and depend inter alia on the concentrations of enzyme and the physiological conditions. Suitable physiological conditions are those necessary to maintain adenosine kinase viability and include temperature, acidity, tonicity and the like. Inhibition of adenosine kinase can be performed, by example, according to standard procedures well known in the art (Yamada, et al., Comp. Biochem. Physiol., (1982), 71B, 367-372), hereby incorporated by reference.

20

15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 400 405 410 415 420 425 430 435 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630 635 640 645 650 655 660 665 670 675 680 685 690 695 700 705 710 715 720 725 730 735 740 745 750 755 760 765 770 775 780 785 790 795 800 805 810 815 820 825 830 835 840 845 850 855 860 865 870 875 880 885 890 895 900 905 910 915 920 925 930 935 940 945 950 955 960 965 970 975 980 985 990 995 1000 1005 1010 1015 1020 1025 1030 1035 1040 1045 1050 1055 1060 1065 1070 1075 1080 1085 1090 1095 1100 1105 1110 1115 1120 1125 1130 1135 1140 1145 1150 1155 1160 1165 1170 1175 1180 1185 1190 1195 1200 1205 1210 1215 1220 1225 1230 1235 1240 1245 1250 1255 1260 1265 1270 1275 1280 1285 1290 1295 1300 1305 1310 1315 1320 1325 1330 1335 1340 1345 1350 1355 1360 1365 1370 1375 1380 1385 1390 1395 1400 1405 1410 1415 1420 1425 1430 1435 1440 1445 1450 1455 1460 1465 1470 1475 1480 1485 1490 1495 1500 1505 1510 1515 1520 1525 1530 1535 1540 1545 1550 1555 1560 1565 1570 1575 1580 1585 1590 1595 1600 1605 1610 1615 1620 1625 1630 1635 1640 1645 1650 1655 1660 1665 1670 1675 1680 1685 1690 1695 1700 1705 1710 1715 1720 1725 1730 1735 1740 1745 1750 1755 1760 1765 1770 1775 1780 1785 1790 1795 1800 1805 1810 1815 1820 1825 1830 1835 1840 1845 1850 1855 1860 1865 1870 1875 1880 1885 1890 1895 1900 1905 1910 1915 1920 1925 1930 1935 1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015 2020 2025 2030 2035 2040 2045 2050 2055 2060 2065 2070 2075 2080 2085 2090 2095 2100 2105 2110 2115 2120 2125 2130 2135 2140 2145 2150 2155 2160 2165 2170 2175 2180 2185 2190 2195 2200 2205 2210 2215 2220 2225 2230 2235 2240 2245 2250 2255 2260 2265 2270 2275 2280 2285 2290 2295 2300 2305 2310 2315 2320 2325 2330 2335 2340 2345 2350 2355 2360 2365 2370 2375 2380 2385 2390 2395 2400 2405 2410 2415 2420 2425 2430 2435 2440 2445 2450 2455 2460 2465 2470 2475 2480 2485 2490 2495 2500 2505 2510 2515 2520 2525 2530 2535 2540 2545 2550 2555 2560 2565 2570 2575 2580 2585 2590 2595 2600 2605 2610 2615 2620 2625 2630 2635 2640 2645 2650 2655 2660 2665 2670 2675 2680 2685 2690 2695 2700 2705 2710 2715 2720 2725 2730 2735 2740 2745 2750 2755 2760 2765 2770 2775 2780 2785 2790 2795 2800 2805 2810 2815 2820 2825 2830 2835 2840 2845 2850 2855 2860 2865 2870 2875 2880 2885 2890 2895 2900 2905 2910 2915 2920 2925 2930 2935 2940 2945 2950 2955 2960 2965 2970 2975 2980 2985 2990 2995 3000 3005 3010 3015 3020 3025 3030 3035 3040 3045 3050 3055 3060 3065 3070 3075 3080 3085 3090 3095 3100 3105 3110 3115 3120 3125 3130 3135 3140 3145 3150 3155 3160 3165 3170 3175 3180 3185 3190 3195 3200 3205 3210 3215 3220 3225 3230 3235 3240 3245 3250 3255 3260 3265 3270 3275 3280 3285 3290 3295 3300 3305 3310 3315 3320 3325 3330 3335 3340 3345 3350 3355 3360 3365 3370 3375 3380 3385 3390 3395 3400 3405 3410 3415 3420 3425 3430 3435 3440 3445 3450 3455 3460 3465 3470 3475 3480 3485 3490 3495 3500 3505 3510 3515 3520 3525 3530 3535 3540 3545 3550 3555 3560 3565 3570 3575 3580 3585 3590 3595 3600 3605 3610 3615 3620 3625 3630 3635 3640 3645 3650 3655 3660 3665 3670 3675 3680 3685 3690 3695 3700 3705 3710 3715 3720 3725 3730 3735 3740 3745 3750 3755 3760 3765 3770 3775 3780 3785 3790 3795 3800 3805 3810 3815 3820 3825 3830 3835 3840 3845 3850 3855 3860 3865 3870 3875 3880 3885 3890 3895 3900 3905 3910 3915 3920 3925 3930 3935 3940 3945 3950 3955 3960 3965 3970 3975 3980 3985 3990 3995 4000 4005 4010 4015 4020 4025 4030 4035 4040 4045 4050 4055 4060 4065 4070 4075 4080 4085 4090 4095 4100 4105 4110 4115 4120 4125 4130 4135 4140 4145 4150 4155 4160 4165 4170 4175 4180 4185 4190 4195 4200 4205 4210 4215 4220 4225 4230 4235 4240 4245 4250 4255 4260 4265 4270 4275 4280 4285 4290 4295 4300 4305 4310 4315 4320 4325 4330 4335 4340 4345 4350 4355 4360 4365 4370 4375 4380 4385 4390 4395 4400 4405 4410 4415 4420 4425 4430 4435 4440 4445 4450 4455 4460 4465 4470 4475 4480 4485 4490 4495 4500 4505 4510 4515 4520 4525 4530 4535 4540 4545 4550 4555 4560 4565 4570 4575 4580 4585

5

adenosine A₁, A_{2A}, and A_{2B} receptor binding, adenosine deaminase activity and adenosine transport.

10

Where the adenosine kinase is located *in situ* or *in vivo*, the inhibiting compound is typically administered to a fluid perfusing the tissue containing the enzyme. That fluid can be a naturally occurring fluid such as blood or plasma or an artificial fluid such as saline, Ringer's solution and the like.

15

Numerous animal models for studying adenosine kinase activity and the effects of inhibiting such activity are well known in the art. By way of example, adenosine kinase inhibitors have been reported to protect rodents (e.g., mice and rats) from experimentally-induced seizure activity (Zhang, G., Murray, T.F., J. Pharmacol. Exp. Ther., 1993, 264, 1415-1424; Murray, T.F., et al., Drug Dev. Res., 1993, 28, 410-415; Kowaluk, E. A., et al., Drug Dev. Res., 1996, 37, 190), hereby incorporated by reference. Other animal models of adenosine kinase activity have been described (See, e.g., Davies, et al., Biochem. Pharmacol., 1984, 33, 347-355; Keil, et al., Eur. J. Pharmacol., 1994, 271, 37-46; Murray, et al., Drug Development Res., 1993, 28, 410-415), hereby incorporated by reference.

20

A method of inhibiting adenosine kinase *in vivo* is particularly useful in mammals such as humans. Administering a therapeutic amount of an inhibitor compound is typically accomplished by the parenteral (e.g., intravenous injection) or oral administration of the compound.

30

By a "therapeutically-effective amount" of the compound of the invention is meant a sufficient amount of the compound to treat adenosine kinase related disorders or those conditions or diseases which are ameliorated or modified by local inhibition of the enzyme which results in an increase in the concentration of adenosine. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention is to be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically-effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, gender and diet of the patient; the time of

50

5

10

administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with specific compound employed; and the like factors well known in the medical arts and well within the capabilities of attending physicians.

15

5 The compounds of the invention were tested in vivo in the hot plate test of analgesia in mammals such as mice. For example, the compounds of examples 6, 79, 104, 130, 133, 134, 137, 205, 246 and 256 in the procedure described directly below were tested thirty minutes after pretreatment with the drugs (30 µmol/kg i.p.) for latency to 10th jump (in seconds). The longer the number of seconds, the more effective the drug at masking the pain felt from the hot plate. Compound 6 resulted in 152 seconds relative to the vehicle alone of 72.8±10.5 seconds (average±standard deviation); compound 79 resulted in 143 seconds; compound 104 resulted in 180 seconds; compound 130 resulted in 158 seconds; compound 133 resulted in 131 seconds; compound 134 resulted in 137 seconds; compound 137 resulted in 159 seconds; compound 205 resulted in 158 seconds, compound 246 resulted in 160 seconds and compound 256 resulted in 143 seconds. Compounds of the invention are therefore potent pain relievers as demonstrated in this animal model.

20

25

30

Mouse Hot Plate Assay

35

40

45

50

20 Male CF1 mice (Charles River) of approximately 25-30 g body weight are pretreated with 10 ml/kg of the test compounds, i.p. or p.o., in groups of 8 animals per dose. At the end of the pretreatment period, the mice are placed in an Omnitech Electronics Automated 16 Animal Hot Plate Analgesia Monitor (Columbus, OH; Model AHP16AN) in individual, 9.8 x 7.2 x 15.3 cm (l x w x h) plastic enclosures on top of a copper plate warmed to 55 °C. Infared sensors located near the top of each enclosure record beam crossings that occur as the mice jump off of the heated surface. Latency times for each jump are automatically recorded, and latency to both the first and tenth jumps are used for data analysis. Mice that do not reach the criteria of 10 jumps by 180 seconds are immediately removed from the hotplate to avoid tissue damage, and they are assigned the maximum value of 180 seconds as their latency to tenth jump.

55

5

10

15

20

25

30

35

40

45

50

Numerous other animal models of adenosine kinase activity have been described [See, e.g., Davies, et al., Biochem. Pharmacol., 33:347-355 (1984); Keil, et al., Eur. J. Pharmacol., 271:37-46 (1994); Murray, et al., Drug Development Res., 28:410-415 (1993)].

5 Compounds of the present invention were also tested in vitro. The results of some representative studies are shown below in Tables 1 below. The Examples provided before the claims are all adenosine kinase inhibitors. The data indicate that the compounds inhibit adenosine kinase and are useful as adenosine kinase inhibitors. The compounds of the invention including compounds of formula I and II with the variables recited herein are 10 also useful as screening tools or as comparative indicators of adenosine kinase inhibition activity relative to unknown inhibitors or potential inhibitors.

Table 1
Inhibition of Adenosine Kinase by Representative Compounds of the Invention

Compound of Example No.	IC ₅₀ (nM)
6	200
15	7
44	50
53	3
56	35
57	1
64	8
79	5
81	3
100	2
104	2
130	1
133	2
134	1
137	5

5

10

15

20

25

30

35

40

45

50

147	150
150	150
170	1
175	300
177	25
201	3
205	3
208	4
246	5
247	3
256	1
270	20
272	>100
274	2
283	8
288	0.3
290	1
291	0.6
292	10
303	1
304	1
306	0.3
308	2
309	0.1
315	0.3
319	1
327	1
330	5
333	2

55

5

10

15

20

25

30

35

40

45

50

336	8
337	4
338	4.5
347	3
351	4
352	5
353	21
354	11
355	4
356	3
357	12
358	60
359	8
360	50
361	5
362	12
363	28
371	6
403	2
431	2
440	3
441	2
464	6
569	8

Additional compounds of the present invention were tested for adenosine kinase inhibition using the above protocol. These compounds exhibited potent inhibition of adenosine kinase with ED₅₀'s ranging from 1 to 500 nM.

5 Carrageenan hyperalgesia Test-Hotbox Assay

55

5

10

This assay may be indicative of a compound's ability to produce analgesia against carrageenan and capsaicin induced hyperalgesia. The assay is further discussed in Hargreaves K, Dubner R, Brown F, Flores C, Joris J (1988), A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. Pain 32: 77-88, hereby fully incorporated by reference.

15

C/D Sprague Dawley rats (Charles River), body weight range 250-350 g, are acclimated in the test room for 30-60 min. before any treatment (habituation). Carrageenan (CARR)(lambda, from Sigma, St. Louis, MO) is dissolved in heated saline at 10 mg/ml. This solution is sonicated and vortexed and then cooled to room temperature.

20

After rats have been habituated they are injected with 100 µl of the CARR solution into the plantar surface (s.c.) of the right hindpaw. A 26 3/8 g needle is used for injection. The insertion of the needle will start at the midline of the foot between the tori and project toward the heel ~0.25 cm . Needle is then slowly removed from the skin to prevent seepage. Test compounds are administered at a time predetermined in relation to CARR

25

injection (typically 1 hour pre CARR administration). The left hindpaw receives no injections. After carrageenan injection the rats are returned to their cages until 30 minutes before testing at which time they are placed in the Hargreaves thermal stimulator apparatus (Hotbox) for a 30 minute habituation period. Testing (thermal stimulation) is then performed. Each rat is tested 3 times (both right and left hindpaw) with approx. 5

30

minute between trials. The standard setting for the thermal stimulator (voltmeter) is 4.5 and the maximum time of exposure is 20.48 seconds. Scoring is based on latency to withdrawal from the thermal stimuli (0-20.48 seconds) The 2 lowest times of the three taken are averaged and the means are then determined for both the right and left paws (n=6 in most cases). Data is analyzed using GB Stat, with ANOVA protected T-tests to

35

determine significant carrageenan effect (right versus left in same animal) and analgesic effect (right drug treated vs. right control). Results are indicated below as ED₅₀ values in micromolar concentration. For those values in nanomolar concentration, the values are designated by "nm".

40

45

30	<u>Compound</u>	<u>ED₅₀ value (micromole/kg)</u>
----	-----------------	---

50

5

	Example 134	0.6
	Example 351	3
	Example 352	3
10	Example 353	3
	Example 354	1
	Example 355	1
15	Example 356	1
	Example 357	3
	Example 359	1
20	Example 534	3

Additional compounds of the present invention were tested in the carrageenan and capsaicin induced hyperalgesia hotbox assay using the above protocol in C/D Sprague Dawley rats. These compounds exhibited ED₅₀'s ranging from 1 to >10 micromolar. Compounds exhibiting less potency in the carrageenan hyperalgesia hotbox assay may require a higher dose or potency may be species dependent.

30

Method of Treating Cerebral Ischemia, Epilepsy,

Nociperception (Nociception) (Pain), Inflammation including conditions such as Septic Shock due to Sepsis Infection.

35

20 In yet another aspect of the present invention a method of treating cerebral ischemia, epilepsy, nociperception or nociception, inflammation including conditions such as septic shock due to sepsis infection in a human or lower mammal is disclosed, comprising administering to the mammal a therapeutically effective amount of a compound of formula I with R¹-R⁴ as defined herein. The preferred compounds are those

40

25 of formula II with the R variables as defined previously. In particular, the present invention relates to a method of treating the above disorders comprising administering a compound of formula II wherein R³ is a substituted aryl or heterocycle moiety wherein the substituent (preferably halogen) is at the meta or 3-position relative to the ring attachment and R⁴ is a substituted heterocycle or aryl moiety wherein the substituent is at the para or

50

5

4-position relative to the ring attachment. The most preferred use is in the treatment of pain.

10

Alterations in cellular adenosine kinase activity have been observed in certain disorders. Adenosine kinase activity was found to be decreased, relative to normal liver, in a variety of rat hepatomas: activity of the enzyme giving a negative correlation with tumor growth rate (Jackson, et al., Br. J. Cancer, 1978, 37: 701-713). Adenosine kinase

15

activity was also diminished in regenerating liver after partial hepatectomy in experimental animals (Jackson, et al., Br. J. Cancer, 1978, 37: 701-713). Erythrocyte Adenosine kinase activity was found to be diminished in patients with gout (Nishizawa, et

20

al., Clin. Chim. Acta 1976, 67: 15-20). Lymphocyte adenosine kinase activity was decreased in patients infected with the human immunodeficiency virus (HIV) exhibiting symptoms of AIDS, and increased in asymptomatic HIV-seropositive and HIV-seronegative high-risk subjects, compared to normal healthy controls (Renouf, et al., Clin.

25

Chem. 1989, 35: 1478-1481). It has been suggested that measurement of adenosine kinase activity may prove useful in monitoring the clinical progress of patients with HIV infection (Renouf, et al., Clin. Chem. 1989, 35: 1478-1481). Sepsis infection may lead to a systemic inflammatory syndrome (SIRS), characterized by an increase in cytokine production, neutrophil accumulation, hemodynamic effects, and tissue damage or death. The ability of adenosine kinase inhibitor to elevate adenosine levels in tissues has been

30

demonstrated to ameliorate syndrome symptoms, due to the known anti-inflammatory effects of adenosine. (Firestein, et al., J. of Immunology, 1994: 5853-5859). The ability of adenosine kinase inhibitors to elevate adenosine levels is expected to alleviate pain states, since it has been demonstrated that administration of adenosine or its analogs results in antinociception or antinociperception. (Swaynok, et al., Neuroscience, 1989, 32:557-569).

40

The following Examples illustrate preferred embodiments of the present invention and are not limiting of the specification and claims in any way.

45

Example 1

30 4-amino-5-(p-dimethylaminophenyl)-7-(p-bromophenyl)pyrido[2,3-d]pyrimidine

50

5

10

A sample of 4-(4-bromophenyl)-3-cyano-6-(4-(dimethylamino)phenyl)pyridine-2-amine (1 g), was suspended in formamide (20 mL), and the reaction was heated to reflux. After about 3 hours, the reaction was complete as monitored by TLC, and the reaction mixture was cooled to room temperature. The product was allowed to precipitate, then recovered by filtration and washed with water. Additional product was recovered from the filtrate. The product was purified by column chromatography eluting with 10% MeOH/CH₂Cl₂ to give the pure title compound. IR (KBr) 3503, 3398, 1731, 1658, 1510, 1467, 1278cm⁻¹; MS m/z 421 (M+H)⁺.

15

20

The 6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino)phenyl)pyridine-2-amine compound was prepared as follows:

25

The reagents, 4-bromoacetophenone (10 mmol, the "R⁴ reagent"), 4-dimethylaminobenzaldehyde (10 mmol, the "R³ reagent"), malononitrile (10 mmol) and ammonium acetate (1.4 g) were added to 25 mL of benzene. The reaction mixture was heated to reflux in a vessel fitted with a Dean-Stork apparatus. After 3.5 hours, the mixture was cooled, and the solvent was removed. The residue was purified by flash chromatography, eluting with methylene chloride, with optional addition of 5% ethyl acetate to the eluant. MS m/z 394 (M+H)⁺.

30

20

Examples 2-156

35

Following the procedures of Example 1, except substituting the appropriate reagents for R⁴ and R³ as indicated in Table 2 below, compounds of Examples 2-156 were prepared.

40

45

50

5

Table 2
Examples 2-156

10

	Ex. No.	Name	R ⁴ Reagent (for 7-position)	R ³ Reagent (for 5-position)	Analytical Data
15	2	4-amino-5-(4-dimethylaminophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylamino-phenyl)-ethanone	4-dimethylamino-benzaldehyde	IR (KBr) 3440, 1615, 1760, 1210cm ⁻¹ ; MS m/z 385 (M+H) ⁺ .
20	3	4-amino-5-(4-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylamino-phenyl)-ethanone	4-methoxybenzaldehyde	IR (KBr) 3330, 1600, 1640, 1780, 1200cm ⁻¹ ; MS m/z, 372(M+H) ⁺ .
25	4	4-amino-5-(4-dimethylaminophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(4-methoxyphenyl)-ethanone	4-dimethylamino-benzaldehyde	IR (KBr) 3660, 1600, 1620, 1510, 1360, 1240 cm ⁻¹ ; MS m/z 372 (M+H) ⁺ .
30	5	4-amino-5-(4-isopropylphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(4-methoxyphenyl)-ethanone	4-isopropyl-benzaldehyde	IR (KBr) 3430, 3360, 1580, 1540 cm ⁻¹ ; MS m/z 371 (M+H) ⁺ .
35					
40					
45					

50

5

10

15

20

25

30

35

40

45

50

	6	4-amino-5-(4-neopentylphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(4-methoxyphenyl)-ethanone	4-neopentylbenzaldehyde	IR (KBr) 3480, 2960, 1580, 1510, 1240 cm ⁻¹ ; MS m/z 399 (M+H) ⁺ .
	7	4-amino-5-(4-butoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(4-methoxyphenyl)-ethanone	4-butoxybenzaldehyde	IR (KBr) 3480, 1600, 1580, 1510, 1240, 1180 cm ⁻¹ ; MS m/z 401 (M+H) ⁺ .
	8	4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;	1-(4-bromophenyl)-ethanone	4-methoxybenzaldehyde	IR (KBr) 3660, 1600, 1680, 1520, 1240cm ⁻¹ ; MS m/z 407(M+H) ⁺ .
	9	4-amino-5-(4-isopropoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(4-methoxyphenyl)-ethanone	4-isopropoxybenzaldehyde	IR (KBr) 3480, 2940, 1600, 1580, 1504 cm ⁻¹ ; MS m/z 386 (M+H) ⁺ .
	10	4-amino-5-(4-butoxyphenyl)-7-(4-N-formylpiperazinylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-N-formylpiperazinylphenyl)-ethanone	4-butoxybenzaldehyde	IR (KBr) 3480, 2940, 1660, 1600, 1580, 1510 cm ⁻¹ ; MS m/z 483 (M+H) ⁺ .

55

5

10

15

20

25

30

35

40

45

50

55

	11	4-amino-5-(4-benzyloxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(4-methoxyphenyl)-ethanone	4-benzyloxybenzaldehyde	IR (KBr) 3480, 3040, 1600, 1580, 1560 cm ⁻¹ ; MS m/z 435 (M+H) ⁺ .
	12	4-amino-5-(4-phenoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(4-methoxyphenyl)-ethanone	4-phenoxybenzaldehyde	IR (KBr) 3456, 3053, 1580, 1558, 1247 cm ⁻¹ ; MS m/z 421 (M+H) ⁺ .
	13	4-amino-5-(4-isopropylphenyl)-7-(4-diethylmalonylallylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-(3-(diethylmalonylallyl)phenyl)-ethanone	4-isopropylbenzaldehyde	IR (KBr) 3480, 2980, 1735, 1580, 1555 cm ⁻¹ ; MS m/z 539 (M+H) ⁺ .
	14	4-amino-5-(4-isopropylphenyl)-7-(4-t-butylacrylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-t-butylacrylphenyl)-ethanone	4-isopropylbenzaldehyde	IR (KBr) 3471, 2957, 1708, 1584, 1556, 1149 cm ⁻¹ ; MS m/z 467 (M+H) ⁺ .
	15	4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3480, 1610, 1580, 1560, 1360, 1200 cm ⁻¹ ; MS m/z 421 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

55

	¹⁶ 4-amino-5-(3,4-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3,4-dimethoxybenzaldehyde	IR (KBr) 3450, 1610, 1580, 1560, 1510 cm ⁻¹ ; MS m/z 402 (M+H) ⁺ .
	¹⁷ 4-amino-5-(3-t-butylacrylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-(3-formylphenyl)acrylic acid t-butyl ester	IR (KBr) 3480, 3400, 1700, 1610, 1580, 1560 cm ⁻¹ ; MS m/z 468 (M+H) ⁺ .
	¹⁸ 4-amino-5-(3-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-methoxybenzaldehyde	IR (KBr) 3475, 1610, 1580, 1560, 1200 cm ⁻¹ ; MS m/z 372 (M+H) ⁺ .
	¹⁹ 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3,5-dimethoxybenzaldehyde	IR (KBr) 3419, 1637, 1600, 1572, 1371, 1202 cm ⁻¹ ; MS m/z 402 (M+H) ⁺ .
	²⁰ 4-amino-5-(3-diethylmalonylallylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	2-[2-(3-formylphenyl)vinyl]malonic acid diethyl ester	IR (KBr) 3480, 1720, 1610, 1580, 1558, 1524, 1360 cm ⁻¹ ; MS m/z 540 (M+H) ⁺ .

5

	²¹ 4-amino-5-(3-vinylpyridinylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-vinylpyridinylbenzaldehyde	IR (KBr) 3480, 1610, 1580, 1560, 1513, 1360 cm ⁻¹ ; MS m/z 385 (M+H) ⁺ .
10				
15	²² 4-amino-5-(3-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-trifluoromethylbenzaldehyde	IR (KBr) 3480, 1610, 1580, 1560, 1360, 1200 cm ⁻¹ ; MS m/z 410 (M+H) ⁺ .
20				
25	²³ 4-amino-5-(3-carboxamidophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-amido-benzaldehyde	IR (KBr) 3480, 1610, 1580, 1380, 1200 cm ⁻¹ ; MS m/z 446 (M+H) ⁺ .
30				
35	²⁴ 4-amino-5-(3-cyanophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-cyano-benzaldehyde	IR (KBr) 3460, 3400, 2210, 1610, 1580, 1554, 1360 cm ⁻¹ ; MS m/z 367 (M+H) ⁺ .
40				
45	²⁵ 4-amino-5-(3-benzyloxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-benzyloxy-benzaldehyde	IR (KBr) 3470, 1640, 1580, 1550, 1515, 1357, 1250 cm ⁻¹ ; MS m/z 448 (M+H) ⁺ .
50				

5

10

15

20

25

30

35

40

50

45

55

	²⁶ 4-amino-5-(3-methoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(4-methoxyphenyl)-ethanone	3-methoxybenzaldehyde	IR (KBr) 3470, 1640, 1580, 1550, 1515, 1357, 1250, 1240, 1180 cm ⁻¹ ; MS m/z 359 (M+H) ⁺ .
	²⁷ 4-amino-5-(3-bromophenyl)-7-(4-butoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(4-butoxyphenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3478, 1610, 1580, 1560, 1515, 1355, 1255, 1240, 1180 cm ⁻¹ ; MS m/z 449 (M+H) ⁺ .
	²⁸ 4-amino-5-(3-(2-pyridyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-(2-pyridyl)benzaldehyde	IR (microscope) 3476, 1609, 1580, 1560, 1358 cm ⁻¹ ; MS m/z 419 (M+H) ⁺ .
	²⁹ 4-amino-5-(3-methylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-methyl-benzaldehyde	IR (microscope) 3400, 1640, 1600, 1580, 1540 cm ⁻¹ ; MS m/z 356 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

	30	4-amino-5-(3-chlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-chlorobenzaldehyde	IR (microscope) 3400, 1600, 1580, 1540 cm ⁻¹ ; MS m/z 376 (M+H) ⁺ .
	31	4-amino-5-(3-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-fluorobenzaldehyde	IR (microscope) 3480, 1640, 1580, 1560 cm ⁻¹ ; MS m/z 360 (M+H) ⁺ .
	32	4-amino-5-(3-bromophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(4-methoxyphenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3485, 1607, 1575, 1550, 1515, 1350, 1255, 1240, 1180, 1030 cm ⁻¹ ; MS m/z 407 (M+H) ⁺ .
	33	4-amino-5-(3-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;	1-(4-bromophenyl)-ethanone	3-methoxybenzaldehyde	IR (microscope) 3450, 1640, 1573, 1555, 1496, 1350, 1260 cm ⁻¹ ; MS m/z 407 (M+H) ⁺ .

55

5

10

15

20

25

30

35

40

45

50

55

	34	4-amino-5-(3-bromophenyl)-7-phenyl pyrido[2,3-d]pyrimidine;	1-phenyl-ethanone	3-bromo-benzaldehyde	IR (KBr) 3480, 1640, 1580, 1560, 1480, 1350, 700 cm ⁻¹ ; MS m/z 377 (M+H) ⁺ .
	35	4-amino-5-(3-bromophenyl)-7-(4-ethylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-ethylphenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3480, 1645, 1580 (broad), 1490, 1380 cm ⁻¹ ; MS m/z 405 (M+H) ⁺ .
	36	4-amino-5-(3-bromophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;	1-(4-bromophenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3480, 1610, 1575, 1540, 1350 cm ⁻¹ ; MS m/z 455 (M+H) ⁺ .
	37	4-amino-5-(3-bromophenyl)-7-(4-cyanophenyl)pyrido[2,3-d]pyrimidine;	1-(4-cyanophenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3480, 2230, 1618, 1580, 1555, 1545, 1350 cm ⁻¹ ; MS m/z 402 (M+H) ⁺ .

5

10

15

20

25

30

35

40

50

55

	38	4-amino-5-(3-bromophenyl)-7-(4-hydroxyphenyl)pyrido[2,3-d]pyrimidine;	1-(4-hydroxyphenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3481, 3060 (broad), 1645, 1580, 1560, 1544, 1360, 1240 1155 cm ⁻¹ ; MS m/z 393 (M+H) ⁺ .
	39	4-amino-5-(3-iodophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-iodo-benzaldehyde	IR (microscope) 3500, 3040, 1640, 1600, 1580, 1560 cm ⁻¹ ; MS m/z 468 (M+H) ⁺ .
	40	4-amino-5-(3-ethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-ethoxy-benzaldehyde	IR (microscope) 3460, 3250, 1640, 1600, 1580, 1560 cm ⁻¹ ; MS m/z 386 (M+H) ⁺ .
	41	4-amino-5-(3-trifluoromethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-trifluoromethoxy-benzaldehyde	IR (microscope) 3480, 1710, 1610, 1580, 1560, 1540 cm ⁻¹ ; MS m/z 426 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

55

	42	4-amino-5-(3,5-dichlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3,5-dichlorobenzaldehyde	IR (microscope) 3500, 3040, 1640, 1600, 1580, 1560 cm ⁻¹ ; MS m/z 411 (M+H) ⁺ .
	43	4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-bromo-4-fluorobenzaldehyde	IR (microscope) 3440, 3015, 1633, 1607, 1583 cm ⁻¹ ; MS m/z 438 (M+H) ⁺ .
	44	4-amino-5-(3-hydroxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-hydroxybenzaldehyde	IR (microscope) 3450, 1640, 1610, 1580, 1560 cm ⁻¹ ; MS m/z 358 (M+H) ⁺ .
	45	4-amino-5-(3-bromophenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-morpholinylphenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3483, 1607, 1578, 1561, 1518, 1355, 1228, 1120 cm ⁻¹ ; MS m/z 462 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

	46	4-amino-5-(3-bromophenyl)-7-(4-piperidinylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-piperidinylphenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3486, 1606, 1561, 1540, 1519, 1353, 1231, 1199, 1128 cm ⁻¹ ; MS m/z 460 (M+H) ⁺ .
	47	4-amino-5-(3-bromophenyl)-7-(4-(imidazol-1-yl)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(imidazol-1-yl)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3481, 1580, 1555, 1525, 1482, 1352, 1303, 1053 cm ⁻¹ ; MS m/z 443 (M+H) ⁺ .
	48	4-amino-5-(3-bromophenyl)-7-(4-chlorophenyl)pyrido[2,3-d]pyrimidine;	1-(4-chlorophenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3470, 1635, 1580, 1560, 1500, 1350, 1090 cm ⁻¹ ; MS m/z 411 (M+H) ⁺ .
	49	4-amino-5-(3-bromophenyl)-7-(4-isopropylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-isopropylphenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3484, 1610, 1579, 1560, 1550, 1483, 1357 cm ⁻¹ ; MS m/z 419 (M+H) ⁺ .

55

5

10

15

20

25

30

35

40

50

55

	50	4-amino-5-(3-bromophenyl)-7-(4-trifluorophenyl)pyrido[2,3-d]pyrimidine;	1-(4-trifluorophenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3481, 3289, 1616, 1579, 1547, 1324, 1312, 1122, 1070 cm ⁻¹ ; MS m/z 445 (M+H) ⁺ .
	51	4-amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-diethylaminophenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3481, 1607, 1578, 1561, 1533, 1353, 1200, 1155 cm ⁻¹ ; MS m/z 448 (M+H) ⁺ .
	52	4-amino-5-(3-bromophenyl)-7-(3,4,5-trimethoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(3,4,5-trimethoxyphenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3485, 1579, 1548, 1507, 1340, 1129 cm ⁻¹ ; MS m/z 467 (M+H) ⁺ .
	53	4-amino-5-(3-(3-methoxybenzyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-(3-methoxybenzyl)-benzaldehyde	IR (KBr) 3425, 1613, 1580, 1558, 1537 cm ⁻¹ ; MS m/z 478 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

	54	4-amino-5-(3-methoxyethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-methoxyethoxybenzaldehyde	IR (KBr) 3469, 1610, 1580, 1560, 1357 cm ⁻¹ ; MS m/z 416 (M+H) ⁺ .
	55	4-amino-5-(3,4-methylenedioxophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3,4-methylenedioxobenzaldehyde	IR (KBr) 3466, 16245, 1579, 1560 cm ⁻¹ ; MS m/z 386 (M+H) ⁺ .
	56	4-amino-5-(3-bromophenyl)-7-(4-ethoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(4-ethoxyphenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3480, 1607, 1579, 1560, 1517, 1360, 1238, 1180 cm ⁻¹ ; MS m/z 421 (M+H) ⁺ .
	57	4-amino-5-(3-bromophenyl)-7-(2'-thiophene)pyrido[2,3-d]pyrimidine;	1-(2-thienyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3470, 1579, 1560, 1547, 1429, 1361 cm ⁻¹ ; MS m/z 383 (M+H) ⁺ .
	58	4-amino-5-(3-bromophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine;	1-(4-fluorophenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3476, 1600, 1580, 1555, 1515, 1350, 1230 cm ⁻¹ ; MS m/z 395 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

	59	4-amino-5-(3-dimethylaminophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-dimethylamino-benzaldehyde	IR (KBr) 3436, 1601, 1580, 1563, 1534, 1200 cm ⁻¹ ; MS m/z 385 (M+H) ⁺ .
	60	4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	benzaldehyde	IR (KBr) 3400, 1600, 1580, 1560, 1530, 1200 cm ⁻¹ ; MS m/z 342 (M+H) ⁺ .
	61	4-amino-5-(3,4,5-trimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3,4,5-trimethoxy-benzaldehyde	IR (KBr) 33460, 1607, 1578, 1127cm ⁻¹ ; MS m/z 432 (M+H) ⁺ .
	62	4-amino-5-(3-bromophenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine;	1-(4-nitrophenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3485, 1618, 1580, 1550, 1520, 1340, 860 cm ⁻¹ ; MS m/z 422 (M+H) ⁺ .
	63	4-amino-5-(3-bromophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;	1-(4-iodophenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3480, 1610, 1575, 1570, 1540, 1350, 1000 cm ⁻¹ ; MS m/z 503 (M+H) ⁺ .

55

5

10

15

20

25

30

35

40

45

50

55

	64	4-amino-5-(3-bromophenyl)-7-(3,4-methylenedioxyphenyl)pyrido[2,3-d]pyrimidine;	1-(3,4-methylenedioxyphenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3485, 1607, 1575, 1545, 1500, 1440, 1350, 1255, 1038 cm ⁻¹ ; MS m/z 421 (M+H) ⁺ .
	65	4-amino-5-(thiophen-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-morpholinylphenyl)-ethanone	thiophene-2-carboxaldehyde	IR (KBr) 3480, 1607, 1580, 1560, 1226 cm ⁻¹ ; MS m/z 390 (M+H) ⁺ .
	66	4-amino-5-(3,5-dimethoxyphenyl)-7-(thiophen-2-yle)pyrido[2,3-d]pyrimidine;	1-(thiophen-2-yl)-ethanone	3,5-dimethoxybenzaldehyde	IR (KBr) 3450, 1640, 1600, 1580, 1560 cm ⁻¹ ; MS m/z 365 (M+H) ⁺ .
	67	4-amino-5-(3-bromophenyl)-7-(4-carboxamidophenyl)pyrido[2,3-d]pyrimidine;	1-(4-carboxamidophenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3481, 1674, 1611, 1577, 1558, 1352 cm ⁻¹ ; MS m/z 420 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

55

	68	4-amino-5-(3-bromophenyl)-7-(4-(2-methoxy)ethoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(4-(2-methoxy)ethoxyphenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3478, 1607, 1580, 1560, 1515, 1357, 1260, 1235, 1180, 1113 cm ⁻¹ ; MS m/z 451 (M+H) ⁺ .
	69	4-amino-5-(3,5-dimethoxyphenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-morpholinylphenyl)-ethanone	3,5-dimethoxy-benzaldehyde	IR (KBr) 3450, 1608, 1580, 1555, 1541, 1230, 1210, 1160 cm ⁻¹ ; MS m/z 444 (M+H) ⁺ .
	70	4-amino-5-(3-trifluoromethylphenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;	1-(thiophene-2-yl)-ethanone	3-trifluoromethyl-benzaldehyde	IR (KBr) 3486, 1620, 1580, 1560, 1325, 1123cm ⁻¹ ; MS m/z 373 (M+H) ⁺ .
	71	4-amino-5-(3-bromophenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-aminophenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3450, 1632, 1605, 1580, 1365 cm ⁻¹ ; MS m/z 393 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

	72	4-amino-5-(3-bromo-4-fluorophenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;	1-(thiophene-2-yl)-ethanone	3-bromo-4-fluoro-benzaldehyde	IR (KBr) 3480, 1640, 1580, 1560, 1500cm ⁻¹ ; MS m/z 401 (M+H) ⁺ .
	73	4-amino-5-(3-bromo-4-fluorophenyl)-7-(2-furanyl)pyrido[2,3-d]pyrimidine;	1-(2-furanyl)-ethanone	3-bromo-4-fluoro-benzaldehyde	IR (KBr) 3460, 1600, 1580, 1560, 1500cm ⁻¹ ; MS m/z 385 (M+H) ⁺ .
	74	4-amino-5-(3,5-dimethoxyphenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;	1-(4-iodophenyl)-ethanone	3,5-dimethoxybenzaldehyde	IR (KBr) 3460, 1604, 1575, 1556, 1541, 1207, 1160 cm ⁻¹ ; MS m/z 485 (M+H) ⁺ .
	75	4-amino-5-(3,5-dimethoxyphenyl)-7-(4-imidazolylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-imidazolylphenyl)-ethanone	3,5-dimethoxybenzaldehyde	IR (KBr) 3459, 1604, 1580, 1556, 1524, 1484, 1304, 1159, 1056 cm ⁻¹ ; MS m/z 425 (M+H) ⁺ .
	76	4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(thiophene-2-yl)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(thiophene-2-yl)phenyl)-ethanone	3,5-dimethoxybenzaldehyde	IR (KBr) 3457, 1602, 1579, 1557, 1207, 1159 cm ⁻¹ ; MS m/z 441 (M+H) ⁺ .

55

5

10

15

20

25

30

35

40

45

50

55

	77	4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(3-pyridyl)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(3-pyridyl)phenyl)-ethanone	3,5-dimethoxybenzaldehyde	IR (KBr) 3452, 1604, 1578, 1558, 1287, 1206, 1159 cm ⁻¹ ; MS m/z 436 (M+H) ⁺ .
	78	4-amino-5-(3-bromophenyl)-7-(4-(4-methylpiperidinyl)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(4-methylpiperidinyl)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3475, 1607, 1577, 1558, 1540, 1356, 1232 cm ⁻¹ ; MS m/z 475 (M+H) ⁺ .
	79	4-amino-5-(3-bromophenyl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-pyrrolidinylphenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3486, 1608, 1577, 1560, 1533, 1353, 1196 cm ⁻¹ ; MS m/z 446 (M+H) ⁺ .
	80	4-amino-5-(4-bromothiophen-2-yl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	4-bromothiophene-2-carboxaldehyde	IR (KBr) 3327, 1604, 1578, 1548, 1521, 1367, 1350, 1202, 820 cm ⁻¹ ; MS m/z 426 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

	81	4-amino-5-(4-bromothiophene-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-morpholinylphenyl)-ethanone	4-bromothiophene-2-carboxaldehyde	IR (KBr) 3460, 1606, 1578, 1558, 1541, 1517, 1232, 824 cm ⁻¹ ; MS m/z 468 (M+H) ⁺ .
	82	4-morpholinyl-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-bromophenyl-benzaldehyde	IR (microscope) 3340, 1603, 1580, 1540 cm ⁻¹ ; MS m/z 490 (M+H) ⁺ .
	83	4-amino-5-(4-(5-bromothiophene-2-yl)phenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-morpholinylphenyl)-ethanone	4-(5-bromothiophene-2-yl-)benzaldehyde	IR (KBr) 3460, 1606, 1580, 1558, 1541, 1517, 1233 cm ⁻¹ ; MS m/z 468 (M+H) ⁺ .
	84	4-amino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	4-bromo-benzaldehyde	IR (microscope) 3480, 3320, 1603, 1580, 1540, 820 cm ⁻¹ ; MS m/z 420 (M+H) ⁺ .
	85	4-amino-5-(3-bromophenyl)-7-(4-(acetylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(acetylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3480 1600, 1580, 1520cm ⁻¹ ; MS m/z 434 (M+H) ⁺ .

55

5

10

20

30

40

45

50

55

	86	4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3300, 1606, 1600, 1580, 1560 cm ⁻¹ ; MS m/z 421 (M+H) ⁺ .
	87	4-amino-5-(3,5-dimethoxyphenyl)-7-(5-pyrimidinylphenyl)pyrido[2,3-d]pyrimidine;	1-(5-pyrimidinylphenyl)-ethanone	3,5-dimethoxy-benzaldehyde	IR (microscope) 3458, 1602, 1579, 1558, 1460, 1414, 1364, 1196, 1058 cm ⁻¹ ; MS m/z 437 (M+H) ⁺ .
	88	4-(4-fluorophenyl)amino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3410, 1605, 1570, 1525, 1503 cm ⁻¹ ; MS m/z 514 (M+H) ⁺ .
	89	4-amino-5-(4-bromothiophene-2-yl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-pyrrolidinylphenyl)-ethanone	4-bromothiophene-2-carboxaldehyde	IR (KBr) 3470, 1609, 1577, 1555, 1520, 1409, 1386, 1350, 1196, 821 cm ⁻¹ ; MS m/z 452 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

55

	90	4-amino-5-(4-bromothiophene-2-yl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;	1-(thiophene-2-yl)-ethanone	4-bromothiophene-2-carboxaldehyde	IR (KBr) 3308, 1606, 1578, 1543, 1526, 1427, 1359 cm ⁻¹ ; MS m/z 389 (M+H) ⁺ .
	91	4-amino-5-(3-bromophenyl)-7-(5-(dimethylamino)thiophene-2-yl)pyrido[2,3-d]pyrimidine;	1-(5-(dimethylamino)thiophene-2-yl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3490, 1581, 1556, 1501, 1481, 1407, 1373, 1072 cm ⁻¹ ; MS m/z 426 (M+H) ⁺ .
	92	4-amino-5-(3-bromo-5-iodophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(dimethylamino)phenyl)-ethanone	3-bromo-5-iodobenzaldehyde	IR (KBr) 3493, 1608, 1562, 1533, 1364, 1350, 1200 cm ⁻¹ ; MS m/z 546 (M+H) ⁺ .
	93	4-amino-5-(3,5-di(trifluoromethyl)phenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(dimethylamino)phenyl)-ethanone	3,5-di(trifluoromethyl)-benzaldehyde	IR (KBr) 3484, 1607, 1580, 1554, 1386, 1280 cm ⁻¹ ; MS m/z 478 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

55

	94	4-amino-5-(3,5-di(trifluoromethyl)phenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-morpholinylphenyl)-ethanone	3,5-di(trifluoromethyl)-benzaldehyde	IR (KBr) 3500, 1643, 1602, 1578, 1554, 1280 cm ⁻¹ ; MS m/z 520 (M+H) ⁺ .
	95	4-amino-5-(3,5-dibromophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(dimethylamino)phenyl)-ethanone	3,5-dibromo-benzaldehyde	IR (KBr) 3440, 1608, 1570, 1559, 1536 cm ⁻¹ ; MS m/z 498 (M+H) ⁺ .
	96	4-amino-5-(3,5-dibromophenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-morpholinylphenyl)-ethanone	3,5-dibromo-benzaldehyde	IR (KBr) 3480, 1607, 1560, 1540, 1225 cm ⁻¹ ; MS m/z 540 (M+H) ⁺ .
	97	4-amino-5-(4-bromothiophene-2-yl)-7-(4-(4-methyl(piperidinyl)phenyl)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(4-methylpiperidinyl)phenyl)-ethanone	4-bromothiophene-2-carboxaldehyde	IR (KBr) 3460, 1608, 1576, 1557, 1540, 1513, 1384, 1353, 1240, 823 cm ⁻¹ ; MS m/z 481 (M+H) ⁺ .
	98	4-amino-5-(3,5-dibromophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(dimethylamino)phenyl)-ethanone	3,5-dibromo-benzaldehyde	IR (KBr) 3486, 1608, 1570, 1559, 1536, 1360, 1350, 1200, 823 cm ⁻¹ ; MS m/z 498 (M+H) ⁺ .

5

10

20

25

30

35

40

45

50

	99	4-amino-5-(3-bromophenyl)-7-(3-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(dimethylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3480, 1601, 1579, 1548, 1483, 1357 cm ⁻¹ ; MS m/z 420 (M+H) ⁺ .
	100	4-amino-5-(3-bromophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-methylsulfonylphenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3486, 1600, 1580, 1550, 1490 cm ⁻¹ ; MS m/z 455 (M+H) ⁺ .
	101	4-amino-5-(3-bromophenyl)-7-(3-methoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(3-methoxyphenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3486, 1605, 1578, 1550, 1492, 1346, 1263 cm ⁻¹ ; MS m/z 407 (M+H) ⁺ .
	102	4-amino-5-(3-bromophenyl)-7-(4-(methylthio)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(methylthio)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3485, 1607, 1578, 1566, 1538, 1350, 1094, 795 cm ⁻¹ ; MS m/z 423 (M+H) ⁺ .
	103	4-amino-5-(3-bromophenyl)-7-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidine;	1-(3,4-dichlorophenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3482, 1634, 1576, 1545, 1488, 1342 cm ⁻¹ ; MS m/z 445 (M+H) ⁺ .

55

5

10

15

20

25

30

35

40

45

50

	104	4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(N-methyl-N-formylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3478, 1672, 1639, 1603, 1579, 1547, 841 cm ⁻¹ ; MS m/z 434 (M+H) ⁺ .
	105	4-amino-5-(3-bromophenyl)-7-(4-methylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-methylaminophenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3488, 1637, 1607, 1587, 1360 cm ⁻¹ ; MS m/z 480 (M+H) ⁺ .
	106	4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-methylsulfonylphenyl)-ethanone	3-bromo-4-fluorobenzaldehyde	IR (KBr) 3489, 1578, 1560, 1496, 1311, 1151, 775 cm ⁻¹ ; MS m/z 473 (M+H) ⁺ .
	107	4-amino-5-(3-bromophenyl)-7-(3-amino-4-methoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(3-amino-4-methoxyphenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3431, 1629, 1606, 1583, 1274 cm ⁻¹ ; MS m/z 422 (M+H) ⁺ .
	108	4-amino-5-(3-bromophenyl)-7-(3-bromo-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(3-bromo-4-(dimethylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3470, 1638, 1570, 1560, 1538, 1480, 1345 cm ⁻¹ ; MS m/z 498 (M+H) ⁺ .

55

5

10

15

20

25

30

35

40

45

50

55

	109	4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(3-methyl-4-(dimethylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3438, 1640, 1605, 1580, 1555, 1368 cm ⁻¹ ; MS m/z 434 (M+H) ⁺ .
	110	4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-trifluoroacetylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-(N-methyl-N-trifluoroacetylaminophenyl)pyrido[2,3-d]pyrimidine;	3-bromo-benzaldehyde	IR (KBr) 3443, 1699, 1635, 1606, 1201 cm ⁻¹ ; MS m/z 502 (M+H) ⁺ .
	111	4-amino-5-(3-bromophenyl)-7-(4-(dimethylamino)-3-fluorophenyl)pyrido[2,3-d]pyrimidine;	1-(4-(dimethylamino)-3-fluorophenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3438, 1638, 1592, 1365 cm ⁻¹ ; MS m/z 438 (M+H) ⁺ .
	112	4-amino-5-(3-bromophenyl)-7-(4-(N-ethyl-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(N-ethyl-N-formylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3477, 1672, 1604, 1580, 1562, 1353 cm ⁻¹ ; MS m/z 448 (M+H) ⁺ .
	113	4,4-bis(acetylamino)-5-(3-bromophenyl)-7-(4-(N-methyl-N-acetylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(N-methyl-N-acetylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3434, 1667, 1635, 1600, 1200 cm ⁻¹ ; MS m/z 532 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

55

	114	4-amino-5-(3-bromophenyl)-7-(4-(N-acetyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(N-acetyl-N-methylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3443, 1667, 1635, 1600, 1200 cm ⁻¹ ; MS m/z 532 (M+H) ⁺ .
	115	4-amino-5-(3-bromophenyl)-7-(4-(N-ethylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(N-ethylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3441, 1633, 1603, 1572, 1368 cm ⁻¹ ; MS m/z 420 (M+H) ⁺ .
	116	4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;	1-(N-methyl-N-(2-methoxyethyl)amino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3439, 1636, 1601, 1529, 1361 cm ⁻¹ ; MS m/z 464 (M+H) ⁺ .
	117	4-amino-5-(3-bromophenyl)-7-(4-(N-isopropylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(N-isopropylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3430, 1632, 1600, 1578, 1530, 1357 cm ⁻¹ ; MS m/z 434 (M+H) ⁺ .
	118	4-amino-5-(3-bromophenyl)-7-(4-N-ethyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-N-ethyl-N-(2-methoxyethyl)amino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3488, 1657, 1604, 1579, 1552, 1118 cm ⁻¹ ; MS m/z 506 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

	119	4-amino-5-(3-bromophenyl)-7-(4-N-(3-methoxypropionyl)-N-isopropylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-N-(3-methoxypropionyl)-N-isopropylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3201, 1679, 1617, 1597, 1576, 1539, 1177, 1117 cm ⁻¹ ; MS m/z 521 (M+H) ⁺ .
	120	4-amino-5-(3-bromophenyl)-7-(4-N-(2-(dimethylamino)ethyl)-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-N-(2-(dimethylamino)ethyl)-N-formylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3475, 1681, 1579, 1351, cm ⁻¹ ; MS m/z 491 (M+H) ⁺ .
	121	4-amino-5-(3-bromophenyl)-7-(4-(N-(2-(dimethylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(N-(2-(dimethylamino)ethyl)amino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3431, 1634, 1601, 1573, 1359 cm ⁻¹ ; MS m/z 463 (M+H) ⁺ .
	122	4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-cyano)ethylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(N-methyl-N-(2-cyano)ethylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3475, 2220, 1660, 1604, 1580, 1560, 1352 cm ⁻¹ ; MS m/z 459 (M+H) ⁺ .
	123	4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(3-methoxy)propionylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(N-methyl-N-(3-methoxy)propionylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3475, 1663, 1604, 1578, 1559, 1352 1114 cm ⁻¹ ; MS m/z 478 (M+H) ⁺ .

55

5

10

15

20

25

30

35

40

45

50

55

	124	4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-formyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(3-methyl-4-(N-formyl-N-methylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3486, 1677, 1607, 1579, 1549, 1351 cm ⁻¹ ; MS m/z 448 (M+H) ⁺ .
	125	4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(3-methyl-4-(N-methylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3433, 1635, 1605, 1585, 1359 cm ⁻¹ ; MS m/z 420 (M+H) ⁺ .
	126	4-amino-5-(3-bromophenyl)-7-(4-(4-methoxy-2-butyloxy)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(4-methoxy-2-butyloxy)phenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3473, 3063, 1710, 1671, 1582, 1564, 1352 cm ⁻¹ ; MS m/z 593 (M+H) ⁺ .
	127	4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-(N-phthalimidyl)acetyl)amino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(N-methyl-N-(2-(N-phthalimidyl)acetyl)amino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3443, 1638, 1606, 1582, 1359cm ⁻¹ ; MS m/z 463 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

55

	128	4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methyl-N-(trifluoroacetyl)amino)phenyl)pyrido[2,3-d]pyrimidine;	1-(3-methyl-4-(N-methyl-N-(trifluoroacetyl)amino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3484, 1701, 1610, 1579, 1559, 1221, 1205, 1151 cm ⁻¹ ; MS m/z 516 (M+H) ⁺ .
	129	4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-acetyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(3-methyl-4-(N-acetyl-N-methylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3484, 1663, 1607, 1574, 1547, 1354 cm ⁻¹ ; MS m/z 462 (M+H) ⁺ .
	130	4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridinyl)pyrido[2,3-d]pyrimidine;	1-(6-dimethylamino-3-pyridinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3428, 1652, 1635, 1606, 1585, 1365 cm ⁻¹ ; MS m/z 421 (M+H) ⁺ .
	131	4-amino-5-(3-cyanophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;	1-(4-methylsulfonylphenyl)-ethanone	3-cyano-benzaldehyde	IR (KBr) 3479, 1638, 1576, 1559, 1303, 1147 cm ⁻¹ ; MS m/z 402 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

	132	4-amino-5-(3-cyanophenyl)-7-(4-(N-methyl-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(N-methyl-N-formylamino)-phenyl)-ethanone	3-cyanobenzaldehyde	IR (KBr) 3418, 2230, 1688, 1674, 1584, 1554, 1114 cm ⁻¹ ; MS m/z 381 (M+H) ⁺ .
	133	4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-formylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine;	1-(6-(N-methyl-N-formylamino)-3-pyridinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3474, 1676, 1577, 1561, 1353, 1130cm ⁻¹ ; MS m/z 435 (M+H) ⁺ .
	134	4-amino-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;	1-(6-morpholinyl-3-pyridinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3487, 3396, 1601, 1580, 1558, 1234cm ⁻¹ ; MS m/z 463 (M+H) ⁺ .
	135	4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methoxyethylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine;	1-(6-(N-methyl-N-methoxyethylamino)-3-pyridinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3476, 3307, 1702, 1683, 1605, 1560, 1116cm ⁻¹ ; MS m/z 465 (M+H) ⁺ .
	136	4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;	1-(6-pyrrolidinyl-3-pyridinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3487, 3396, 1601, 1580, 1558, 1234 cm ⁻¹ ; MS m/z 447 (M+H) ⁺ .

55

5

10

15

20

25

30

35

40

45

50

55

	137	4-amino-5-(3-bromophenyl)-7-(2-(dimethylamino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;	1-(2-(dimethylamino)-5-pyrimidinyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3442, 1640, 1604, 1577, 1536, 1408, 1367, 1348 cm ⁻¹ ; MS m/z 422 (M+H) ⁺ .
	138	4-amino-5-(3-bromophenyl)-7-(2-(N-methoxyethyl-N-methyl amino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;	1-(2-(N-methoxyethyl-N-methyl amino)-5-pyrimidinyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3439, 1640, 1606, 1587, 1556, 1537, 1374, 1347 cm ⁻¹ ; MS m/z 466 (M+H) ⁺ .
	139	4-amino-5-(3-bromophenyl)-7-(2-(N-formyl-N-methyl amino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;	1-(2-(N-formyl-N-methyl amino)-5-pyrimidinyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3472, 1687, 1583, 1565, 1459, 1353, 1142, 988 cm ⁻¹ ; MS m/z 436 (M+H) ⁺ .
	140	4-amino-5-(3-bromophenyl)-7-(2-(N-methylamino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;	1-(2-(N-methylamino)-5-pyrimidinyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3483, 1605, 1550, 1346 cm ⁻¹ ; MS m/z 408 (M+H) ⁺ .

5

	141	4-amino-5-(3-bromophenyl)-7-(2-(1-pyrrolidinyl)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;	1-(2-pyrrolidinyl-5-pyrimidinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3468, 1600, 1581, 1552, 1527, 1482, 1330 cm ⁻¹ ; MS m/z 448 (M+H) ⁺ .
10	142	4-amino-5-(3-bromophenyl)-7-(2-(1-morpholinyl)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;	1-(2-morpholinyl-5-pyrimidinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3434, 1637, 1608, 1585, 1335, cm ⁻¹ ; MS m/z 463 (M+H) ⁺ .
15	143	4-amino-5-(3-bromophenyl)-7-(6-(2-oxo-3-oxazolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;	1-(6-(2-oxo-3-oxazolidinyl)-3-pyridinyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3473, 1762, 1583, 1571, 1562, 1491, 1477, 1402, 1348, 1217 cm ⁻¹ ; MS m/z 463 (M+H) ⁺ .
20	144	4-amino-5-(3-bromophenyl)-7-(2-pyridyl)pyrido[2,3-d]pyrimidine;	1-(2-pyridyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3427, 3017, 1601, 783 cm ⁻¹ ; MS m/z 351/353 (M+H) ⁺ .
25	145	4-amino-5-(3-bromophenyl)-7-(3-pyridyl)pyrido[2,3-d]pyrimidine;	1-(3-pyridyl)-ethanone	3-bromo-benzaldehyde	IR (microscope) 3434, 3042, 1634, 1372 cm ⁻¹ ; MS m/z 351/353 (M+H) ⁺ .
30					
35					
40					
45					

50

5

10

15

20

25

30

35

40

45

50

	146	4-amino-5-(3-(thiophen-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-(thiophen-2-yl)-benzaldehyde	IR (microscope) 3482, 2922, 1578, 1356 cm ⁻¹ ; MS m/z 420/422 (M+H) ⁺ .
	147	4-amino-5-(3-(furan-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-(furan-2-yl)-benzaldehyde	IR (microscope) 3479, 3104, 1559, 1356 cm ⁻¹ ; MS m/z 420/422 (M+H) ⁺ .
	148	4-amino-5-(3-(3-methoxyphenyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	3-(3-methoxyphenyl)-benzaldehyde	IR (microscope) 3477, 2924, 1579, 1356 cm ⁻¹ ; MS m/z 420/422 (M+H) ⁺ .
	149	4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;	1-(4-dimethylaminophenyl)-ethanone	benzaldehyde	IR (microscope) 3477, 3298, 1580, 1355 cm ⁻¹ ; MS m/z 315 (M+H) ⁺ .
	150	4-amino-5-(3-chlorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(morpholinyl)phenyl)-ethanone	3-chloro-benzaldehyde	IR (microscope) 3480, 3056, 1579, 1356 cm ⁻¹ ; MS m/z 391 (M+H) ⁺ .
	151	4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(morpholinyl)phenyl)-ethanone	3-bromo-4-fluoro-benzaldehyde	IR (microscope) 3491, 3044, 1560, 1230 cm ⁻¹ ; MS m/z 453 (M+H) ⁺ .

55

5

10

15

20

25

30

35

40

45

50

55

	152	4-amino-5-(3-chlorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;	1-(4-iodophenyl)-ethanone	3-chloro-benzaldehyde	IR (microscope) 3478, 3280, 1539, 1350 cm ⁻¹ ; MS m/z 432 (M+H) ⁺ .
	153	4-amino-5-(3-chlorophenyl)-7-(4-(thiophen-2-yl)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(thiophen-2-yl)phenyl)-ethanone	3-chloro-benzaldehyde	IR (microscope) 3484, 3055, 1560, 1354 cm ⁻¹ ; MS m/z 459 (M+H) ⁺ .
	154	4-amino-5-(3-chlorophenyl)-7-(4-(5-pyrimidinyl)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(5-pyrimidinyl)phenyl)-ethanone	3-chloro-benzaldehyde	IR (microscope) 3477, 3040, 1578, 1351 cm ⁻¹ ; MS m/z 459 (M+H) ⁺ .
	155	4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;	1-(4-iodophenyl)-ethanone	3-bromo-4-fluoro-benzaldehyde	IR (microscope) 3444, 3048, 1607, 1356 cm ⁻¹ ; MS m/z 494/496 (M+H) ⁺ .
	156	4-amino-5-(4-bromothiophene-2-yl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;	1-(4-methoxyphenyl)-ethanone	4-bromothiophene-2-carboxaldehyde	IR (microscope) 3460, 3300, 2900-3100, 1700, 1580, 1510 cm ⁻¹ ; MS m/z 413 (M+H) ⁺ .

Example 157

5

4-amino-5-(3-bromophenyl)methyl-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine hydrochloride

10

A mixture of 3-cyano-4-(3-bromophenyl)methyl-6-(4-

15

(dimethyl)aminophenyl)pyridine-2-amine (1.58 g) and ammonium sulfate (40 mg) in triethyl orthoformate was heated at reflux for 2 hours. The reaction mixture was cooled and added to a mixture of 8 g of ammonia in 150 mL of ethanol. After 16 hours at 25 °C,

20

the reaction was heated at reflux for two hours, and the solvent was removed in vacuo. The residue was purified by chromatography, then converted to the hydrochloride salt by treatment with ether/HCl, followed by drying to give the title compound.

25

The 3-cyano-4-(3-bromophenyl)methyl-6-(4-(dimethyl)aminophenyl)pyridine-2-amine was prepared by a four-step procedure as follows:

30

step 157a: preparation of 3-bromophenylacetaldehyde (the "R³ reagent")

35

15 To a solution of ethyl 3-bromophenylacetate (10.2 g, US patent 2,624,731 (1950)) in 230 mL of dichloromethane was added 42 mL of 1M Dibal-H in toluene at -78 °C with stirring. After 40 minutes at -78 °C, 10 mL of methanol was added, and the reaction allowed to warm to room temperature and partitioned between 50 mL of dichloromethane and 1200 mL of saturated aqueous potassium sodium tartrate. The organic layer was dried over sodium sulfate and the aldehyde used immediately in the next step without purification.

40

step 157b: preparation of α-(triphenylphosphonium)-4-(dimethylamino)phenylethan-1-one chloride

45

25 Following the procedure of Fukui et al. (J. Org. Chem. 33: 3594-3507 (1968)), α-bromo-(4-dimethylaminophenyl)ethan-1-one (the "R⁴ reagent", CAS #37904-72-6; Chem. Abst. (1956), 864) was treated with triphenylphosphine in triethylamine and acetonitrile. The α-bromo-(4-dimethylaminophenyl)ethan-1-one was prepared by bromination with bromine in hydrobromic acid according to the method of Suzuki et al (J. Pharm. Soc.

50

5

Japan. (1955), 75:54. Removal of solvent and recrystallization from methanol/ethyl acetate/toluene gave the title product as a white powder.

10

step 157c: preparation of 1-(4-(dimethylamino)phenyl)-4-(3-bromophenyl)-but-2-en-1-one

15

5 20 g of α -(triphenylphosphonium)-4-(dimethylamino)phenylethan-1-one chloride (from step b) was partitioned between dichloromethane and 50 mL of 2N NaOH. The organic phase was dried over sodium sulfate and concentrated in vacuo. The residue was mixed with 3-bromophenylacetaldehyde (from step a) for 24 hours at 25 °C. The mixture was purified by chromatography to give 8.35 g (61%) of a cis/trans mixture of the title compound. The cis/trans mixture was taken to the next step without separation of the isomers.

20

25

step 157d: preparation of 3-cyano-4-(3-bromophenyl)methyl-6-(4-(dimethyl)aminophenyl)pyridine-2-amine

30

15 A mixture of 1-(4-(dimethylamino)phenyl)-4-(3-bromophenyl)-but-2-en-1-one chloride (3.85 g, from step c), ammonium acetate (2.6 g) and malononitrile (739 mg) in 3 mL of dimethoxyethane and 22 mL of ethanol was heated at 115 °C for 5 hours, then cooled and worked up by partitioning between dichloromethane and water. The residue obtained on concentration of the organic phase was purified by flash chromatography to give the title compound.

35

Examples 158-174

40

Following the procedures of Example 157, except substituting the appropriate reagents for the R⁴ and R³ reagents of Example 157 as indicated in Table 3 below, 25 compounds of Examples 158-174 were prepared. The treatment with aqueous HCl was omitted, and the free bases were obtained except as indicated.

45

In Examples 167-174, the formamide or formamidine acetate (added periodically until the reaction was complete) treatment was replaced by treatment with triethyl orthoformate at reflux in the presence of a catalytic amount of ammonium sulfate, 30 followed by cooling to 25 °C and addition of excess ammonia in ethanol. After 24 hours,

50

5

10

the precipitated amidine compound was filtered and washed with hexanes, then dried under vacuum. The amidine compound was then heated in 1,2-dichlorobenzene at 120-180 °C for 1-8 hours. The reaction mixture was cooled to room temperature and purified by chromatography, and the product was recrystallized if necessary (chloroform in methanol).

15

10

Table 3
Examples 158-187

20

25

30

35

40

45

Ex. No.	Name	R ⁴ Reagent (for 7-position)	R ³ Reagent (for 5-position)	Analytical Data
158	4-amino-5-(2-phenylethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine	1-(4-diethylaminophenyl)-ethanone	3-phenyl-propionaldehyde	IR (KBr) 3340,3240- 2800,1600,1580,1540; H. Res. MS m/z 398.2343 (M+H) ⁺ .
159	4-amino-5-(2-methylpropyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine	1-(4-diethylaminophenyl)-ethanone	3-methyl-butanaldehyde	IR (KBr) 3550,3410,3320, 3240- 2800,1605,1580,1560 H. Res. MS m/z 350.2357 (M+H) ⁺ .
160	4-amino-5-(butyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine	1-(4-diethylaminophenyl)-ethanone	pentanaldehyde	IR (KBr) 3450,3300,3200- 2800,1660,1610,1580,1540 H. Res. MS m/z 350.2354 (M+H) ⁺ .

50

55

5

10

15

20

25

30

35

40

45

50

55

	161	4-amino-5-(2-(4-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine	1-(4-diethylaminophenyl)-ethanone	4-(4-bromophenyl)-propionaldehyde	IR (KBr) 3500,3300,3200-3000,1650,1615,1580 H. Res. MS m/z 478.1429 (M+H)*.
	162	4-amino-5-(butyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	pentanal	IR (KBr) 3400,3350,3200-2900,1650,1620,1580,1570 H. Res. MS m/z 322.2032 (M+H)*.
	163	4-amino-5-(2-(3-cyanophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	3-cyanophenyl-acetaldehyde	IR (KBr) 2850-3550,2220,1610,1580,1560,1540 MS m/z 381 (M+H)*.
	164	4-amino-5-(2-(N-carbobenzyloxy)aminooethyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	3-(N-carbobenzyloxy)aminopropionaldehyde	IR (KBr) 3000-3500,1710,1690,1650,1590 H. Res. MS m/z 443.2184 (M+H)*.
	165	4-amino-5-(cycloheptyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	cycloheptane-carboxaldehyde	IR (KBr) 3500,3250,3100,2950,2850,1620,1575 H. Res. MS m/z 362.2349 (M+H)*.

5

10

15

20

25

30

35

40

45

50

55

	166	4-amino-5-(2-(5-chloro-2-(thiophen-3-yl)phenylmethyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	** procedure of Example 173, using 3-thiophenylboronic acid	IR (KBr) 3200-3450,2950-3100,1605,1580,1550 H. Res. MS m/z 472.1363 (M+H) ⁺ .
	167	4-amino-5-(pentyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine	1-(4-diethylaminophenyl)-ethanone	hexanal	IR (KBr) 3430,3320,3240-2800,1580,1560,1540,1350; mp. 211-214; MS m/z 364 (M+H) ⁺ ; H. Res. MS m/z 364.2506 (M+H) ⁺ .
	168	4-amino-5-hexyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine	1-(4-diethylaminophenyl)-ethanone	heptanal	IR (KBr) 3440,3310,3240-2800,1580,1560,1540,1350; mp. 215-217; MS m/z 378 (M+H) ⁺ ; H. Res. MS m/z 378.2654 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

	169	4-amino-5-(2-(3-bromophenyl)ethyl)-7-(4-diethylaminophenyl)-pyrido[2,3-d]pyrimidine	1-(4-diethylaminophenyl)-ethanone	3-(3-bromophenyl)-propionaldehyde	IR (KBr) 3640-3240,3200-2800,1580,1555,1535,1345; mp. 201-202; MS m/z 476/478 (M+H) ⁺ ; H. Res. MS m/z 476.1448 (M+H) ⁺ .
	170	4-amino-5-((2-bromophenyl)methyl)-7-(4-diethylaminophenyl)-pyrido[2,3-d]pyrimidine	1-(4-diethylaminophenyl)-ethanone	2-(2-bromophenyl)-acetaldhyde	IR (KBr) 3640-3240,3240-2800,1580,1555,1540,1350; mp. 130-133; MS m/z 462/464 (M+H) ⁺ ; H. Res. MS m/z 462.1297 (M+H) ⁺ .
	171	4-amino-5-cyclopropyl-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	cyclopropanecarboxaldehyde	IR (KBr) 3490,3290,3240-2760,1610,1580,1540,1375; mp. 235-237; MS m/z 462/464 (M+H) ⁺ ;
	172	4-amino-5-cyclohexyl-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	cyclohexanecarboxaldehyde	IR (KBr) 3640-3000,2980-2760,1610,1580,1540,1345; mp. 231-234; MS m/z 462/464 (M+H) ⁺ ;

55

5

10

15

20

25

30

	173	4-amino-5-((2-bromo-5-chlorophenyl)methyl)-7-(4-diethylaminophenyl)-pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	2-(2-bromo-5-chlorophenyl)-acetaldehyde	IR (KBr) 3460,3220- 2760,1610,1575,15 35,1365; mp. 185- 187; MS m/z 462/464 (M+H) ⁺ ;
	174	4-amino-5-methyl-7-(4-diethylaminophenyl)-pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	acetaldehyde	IR (KBr) 3640- 3250,3250- 2760,1610,1585,15 60,1350; mp. 238- 246; MS m/z 462/464 (M+H) ⁺ ;

* prepared from the compound of Example 157 by reaction with Pd(PPh₃)₄ and zinc cyanide in DMF under Suzuki reaction conditions.

** prepared from the compound of Example 173 by reaction with 2-thiopheneboronic acid, Pd(PPh₃)₄ and aqueous sodium carbonate under Suzuki reaction conditions.

5

Examples 175-188

35

Following the procedures of Example 1, except substituting the appropriate reagents for the R⁴ and R³ reagents of Example 1 as indicated in Table 4 below, compounds of Examples 175-188 were prepared. The treatment with aqueous HCl was omitted, and the free bases were obtained except as indicated.

40

15

Table 4
Examples 175-188

45

Ex. No.	Name	R ⁴ Reagent (for 7-position)	R ³ Reagent (for 5-position)	Analytical Data
------------	------	--	--	-----------------

50

5

10

15

20

25

30

35

40

45

50

	175	4-amino-5-(2,3-methylenedioxyphenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	2,3-methylenedioxobenzaldehyde	IR (KBr) 3500-2500, 1595, 1580, 1375; mp. 290-305;
	176	4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	3-fluoro-5-trifluoromethylbenzaldehyde	IR (KBr) 3500, 3440-3240, 3200-2800, 1610, 1580, 1560, 1540, 1370; mp. 293-296; MS m/z 428 (M+H) ⁺ ; H. Res. MS m/z 428.1509 (M+H) ⁺ .
	177	4-amino-5-(2-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	2-bromo-benzaldehyde	IR (KBr) 3480, 3440-3240, 3200-2800, 1610, 1575, 1555, 1535, 1355; mp. 261-263; MS m/z 420/422 (M+H) ⁺ ; H. Res. MS m/z 420.0823 (M+H) ⁺ .

55

5

10

15

20

25

30

35

40

45

50

55

	178	4-amino-5-(3,5-dimethylphenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	3,5-dimethylbenzaldehyde	IR (KBr) 3480,3440- 3240,3200- 2800,1610,1575,15 55,1535,1360; mp. 284-286; MS m/z 370 (M+H) ⁺ ; H. Res. MS m/z 370.2036 (M+H) ⁺ .
	179	4-amino-5-(3,4-dichlorophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	3,4-dichlorobenzaldehyde	IR (KBr) 3490,3440- 3240,3200- 2800,1610,1575,15 60,1535,1355; mp. 288-291; MS m/z 410/412 (M+H) ⁺ ; H. Res. MS m/z 410.0948 (M+H) ⁺ .
	180	4-amino-5-(4-fluoro-3-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	4-fluoro-3-trifluoromethylbenzaldehyde	IR (KBr) 3500,3440- 3240,3200- 2800,1610,1580,15 60,1540,1505,1360; mp. 254-257; MS m/z 428 (M+H) ⁺ ; H. Res. MS m/z 428.1487 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

55

	181	4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-morpholinylphenyl)-pyrido[2,3-d]pyrimidine	1-(4-morpholinylphenyl)-ethanone	3-bromo-5-methoxybenzaldehyde	IR (KBr) 3470,3440-3240,3200-2800,1605,1580,1560; mp. 257-260; MS m/z 492/494 (M+H) ⁺ .
	182	4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-pyrrolidinylphenyl)-pyrido[2,3-d]pyrimidine	1-(4-pyrrolidinylphenyl)-ethanone	3-bromo-5-methoxybenzaldehyde	IR (KBr) 3470,3440-3240,3200-2800,1610,1580,1560,1540,1355; mp. 250; MS m/z 476/478 (M+H) ⁺ .
	183	4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-piperidinylphenyl)-pyrido[2,3-d]pyrimidine	1-(4-piperidinylphenyl)-ethanone	3-bromo-5-methoxybenzaldehyde	IR (KBr) 3470,3440-3240,3200-2800,1565; mp. 224-244; MS m/z 490/492 (M+H) ⁺ ;

5

10

15

20

25

30

35

40

45

50

	184	4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	3-bromo-5-methoxybenzaldehyde	IR (KBr) 3470,3420-3240,3200-2800,1610,1575,1555,1535,1355; mp. 262-266; MS m/z 450/452 (M+H) ⁺ ; H. Res. MS m/z 450.0944 (M+H) ⁺ .
	185	4-amino-5-(3-methylthiophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	3-methylthio-benzaldehyde	IR (KBr) 3460,3420-3240,3200-2800,1605,1575,1560,1535,1355; mp. 184-220; MS m/z 388 (M+H) ⁺ ; H. Res. MS m/z 388.1586 (M+H) ⁺ .
	186	4-amino-5-(3-bromo-5-methoxyphenyl)-7-(thiophene-2-yl)-pyrido[2,3-d]pyrimidine	1-(thiophene-2-yl)-ethanone	3-bromo-5-methoxybenzaldehyde	IR (KBr) 3470,3350-2200,1700,1640,1580,1435,1365,1270; mp. 246-249; MS m/z 413/415 (M+H) ⁺ ; H. Res. MS m/z 413.0069 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

	187	4-amino-5-(2,3-dimethoxyphenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine ***	1-(4-dimethylaminophenyl)-ethanone	2,3-dimethoxybenzaldehyde	IR (KBr) 3480,3440- 3240,3200- 2800,1610,1580,15 50,1530,1360; mp. 222-225; MS m/z 402 (M+H) ⁺ ; H. Res. MS m/z 402,1922 (M+H) ⁺ .
	188	4-amino-5-(3-methylsulfonylphenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	3-methylsulfonylbenzaldehyde	IR (KBr)3490,3400- 2800,1610,1580,15 55,1535,1355; mp. 245~270; MS m/z 420 (M+H) ⁺ ; H. Res. MS m/z 420,1493 (M+H) ⁺ .

Example 1894-acetylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine

- 5 A suspension of 4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine (from Example 15, 0.28 g, 0.67 mole) in pyridine (3 mL) was treated with acetic anhydride (0.10 g, 1.0 mmol) and the reaction mixture was stirred for 4 hours at 25 °C. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography (SiO₂, EtOAc/hexanes) to provide the title compound (0.23 g, 73% theoretical): IR (KBr) 3368, 3048, 1695, 1567; MS m/z 462/464 (M+H)⁺.

Examples 190-198

5

Following the procedures of Example 189, except substituting the appropriate acylating reagent for the acetic anhydride of Example 189 as indicated in Table 5 below, compounds of Examples 190-198 were prepared.

10

15

5

Table 5Examples 190-198

Ex. No.	Name	Acyling Reagent	Analytical Data
190	4-formylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine--190	acetic anhydride and formic acid	IR (KBr) 3382, 3047, 1704, 1570; MS m/z 448/450 (M+H) ⁺ .
191	4-(methoxyacetyl)amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)-pyrido[2,3-d]pyrimidine	methoxyacetyl chloride	IR (KBr) 3344, 3044, 1731, 1561; MS m/z 492/494 (M+H) ⁺ .
192	4-trifluoroacetylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	trifluoroacetic anhydride	IR (KBr) 3426, 3072, 1610, 1578; MS m/z 516/518 (M+H) ⁺ .
193	4-pentanoylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	pentanoyl chloride	IR (KBr) 3408, 2954, 1699, 1569; MS m/z 504/506 (M+H) ⁺ .
194	4-benzoylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	benzoic anhydride	IR (KBr) 3420, 3056, 1606, 1583; MS m/z 524/526 (M+H) ⁺ .

50

5

10

15

20

25

30

195	4-(N-BOC-glycyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	N-BOC-glycyl-imidazole	IR (KBr) 3362, 2975, 1719, 1570; MS m/z 577/579 (M+H) ⁺ .
196	4-(N-phthalimidylglycyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	N-phthalimidyl-glycyl-chloride	IR (KBr) 3408, 2927, 1719, 1570; MS m/z 607/609 (M+H) ⁺ .
197	4-(ethoxycarbonyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	diethyl dicarbonate	IR (KBr) 3405, 2987, 1738, 1569; MS m/z 492/494 (M+H) ⁺ .
198	4-(ethylaminocarbonyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine	ethyl isocyanate	IR (KBr) 3405, 3053, 1701, 1548; MS m/z 491/493 (M+H) ⁺ .

Example 1994-allylamino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl) pyrido [2,3-d] pyrimidine

35

The product was prepared by treating a solution of 4-chloro-5-(p-dimethylaminophenyl)-7-(p-bromophenyl)pyrido[2,3-d]pyrimidine in CH₂Cl₂-TEA with allylamine and heating the resulting mixture at reflux for 1 hour. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography (SiO₂, EtOAc/hexanes) to provide the title compound IR (KBr) 3437, 1564, 1355, 1195; MS m/z 460/462 (M+H)⁺.

40

10

45

The 4-chloro-5-(p-dimethylaminophenyl)-7-(p-bromophenyl)pyrido [2,3-d]pyrimidine was prepared as follows.

A sample of 4-(4-bromophenyl)-3-cyano-6-(4-(dimethylamino)phenyl)pyridine-2-amine (from Example 1, 5.0 g, 12.7 mmol) in 20 mL of H₂SO₄ was heated at 80 °C for 30 min.

50

55

5

10

15

20

25

minutes. Ice was added, and the reaction mixture was neutralized with aqueous NaOH. The resulting crude 3-carboxamide was collected by filtration, triturated with EtOAc-hexanes, then dried under reduced pressure (4.95 g, 95% theoretical). A solution of the carboxamide (4.25 g, 10.3 mmol) in triethylorthoformate (20 mL) was treated with p-toluenesulfonic acid (catalytic) and the reaction mixture was warmed at 80 °C for 4 hours. The volatiles were removed and the crude bicyclic 4-hydroxyl-5-(p-dimethylaminophenyl)-7-(p-bromophenyl)pyrido[2,3-d]pyrimidine product was suspended in POCl₃ (15 mL) then warmed at 100 °C for 2 hours. The POCl₃ was removed under reduced pressure to provide crude 4-chloro-5-(p-dimethylaminophenyl)-7-(p-bromophenyl)pyrido[2,3-d]pyrimidine. The invention therefore relates to intermediate compounds of formula III wherein X is selected from hydroxyl or halogen and the remaining variables are the same as in formula I or II.

30

35

40

Example 200

15 4-(2-(N,N-dimethylamino)ethylamino)-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido [2,3-d] pyrimidine trihydrochloride

The product was prepared by treating a solution of 4-chloro-5-(p-dimethylaminophenyl)-7-(p-bromophenyl)pyrido[2,3-d]pyrimidine (prepared as in Example 199) in CH₂Cl₂-TEA with the 2-(dimethylamino)ethylamine and heating the resulting mixture at reflux for 1 hour. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography (SiO₂, EtOAc/hexanes) to provide the title compound. The product was treated with excess 2M HCl (aq) followed by lyophilization to give the product as the trihydrochloride salt; IR (KBr) 3385, 1561, 1356, 1197; MS m/z 491/493 (M+H)⁺.

25

Example 201

45 4-(4-(N,N-dimethylamino)butylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl) pyrido [2,3-d] pyrimidine tetrahydrochloride

The product was prepared by treating a solution of 4-amino-5-(p-dimethylaminophenyl)-7-(p-bromophenyl)pyrido[2,3-d]pyrimidine in CH₂Cl₂-TEA

50

55

5

10

with the 4-(dimethylamino)butylamine and heating the resulting mixture at reflux for 1 hour. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography (SiO₂, EtOAc/hexanes). The product was treated with excess 2M HCl (aq) followed by lyophilization to give the product as the tetrahydrochloride salt: IR (KBr) 3439, 1567, 1356, 1196; MS m/z 519/521 (M+H)⁺.

15

Example 2024-(N-allyl-N-formylamino)-5-(4-dimethylaminophenyl)-7-(p-bromophenyl)pyrido[2,3-d]pyrimidine

20

25

30

A sample of the compound from Example 190 above, 4-formylamino-5-(2-phenylethyl)-7-(4-diethylaminophenyl)-pyrido[2,3-d]pyrimidine (0.27 g, 0.6 mmol) in 3 mL of a 4:1 mixture of THF and DMF at 0°C was treated with NaH (60% dispersion, 36 mg, 0.9 mmol) and the solution was stirred for 0.5 hour. Allyl bromide (0.29 g, 2.4 mmol) was added, and the reaction mixture was stirred for an additional 0.5 hour. Aqueous workup followed by flash chromatography provided the title compound: LRMS m/z 488/490. IR (cm⁻¹) 3428, 2910, 1696, 1551, 1362, 1193.

20

Example 203

35

4-diacetylamino-5-(4-dimethylaminophenyl)-7-(p-bromophenyl)-pyrido[2,3-d]pyrimidine

This compound was isolated as a minor product from the reaction mixture of Example 190 above: LRMS m/z 504/506. IR (cm⁻¹) 2922, 1726, 1550, 1360, 1197.

25

Example 204

45

4-amino-5-(3-bromophenyl)-7-(5-amino-2-pyridyl)pyrido[2,3-d]pyrimidine

30

A solution of 5-aminopyridine-2-ethanone (1.15 g, 8.45 mmol), 3-bromobenzaldehyde (1.70 g, 9.2 mmol), malononitrile (0.61 g, 9.2 mmol), and

50

5

10

15

20

25

30

35

40

45

50

55

ammonium acetate (1.15 g, 15 mmol) in 25 mL of benzene was heated at reflux with azeotropic removal of water. After 6 hours the reaction mixture was concentrated, and the desired intermediate (1.82 g, 49%) was isolated following flash chromatography (SiO₂, EtOAc-CH₂Cl₂). LRMS m/z 366/368. The intermediate was suspended in 15 mL of formamide, and the reaction mixture was heated at 180 °C for 4 hours. The solution was cooled to 25 °C, 10 mL of 4M HCl (aq) was added, and the mixture was stirred for 1 hour. The aqueous solution was neutralized with NaOH (aq), and the precipitate was collected by filtration. The title compound (1.3 g, 68%) was isolated following flash chromatography of the precipitate: LRMS m/z 393/395; IR (cm⁻¹) 3481, 3161, 1620, 1573, 1483, 1359.

The 5-aminopyridine-2-carboxaldehyde starting material was prepared as follows:

204a. 5-amino-2-bromopyridine

A solution of 2-bromo-5-nitropyridine (5.1 g, 25 mmol) in 50 mL of a 10:1

mixture of acetic acid and water was treated with iron powder (7.8 g, 140 mmol) in several portions over 20 minutes. After an additional 30 minutes the volatiles were removed under reduced pressure, and the residue was quenched with 5% aqueous sodium carbonate. The aqueous solution was extracted with methylene chloride, and the combined organic layer was dried (sodium sulfate) then concentrated in vacuo to provide the desired product as a white solid (4.25 g, 98%).

204b. 5-aminopyridine-2-ethanone

A sample of 5-amino-2-bromopyridine (4.25 g, 24 mmol), PdCl₂(PPh₃)₂ (0.34 g, 2 mole%), CuI (0.09 g, 2 mole%), and trimethylsilylacetylene (3.0 g, 31 mmol) were dissolved in 100 mL of a 4:1 mixture of triethylamine and acetonitrile, and the reaction mixture was stirred 24 hours at 25 °C. The reaction mixture was concentrated, and the residue was dissolved in 100 mL of a 10:1 mixture of acetone and water. Hg(O₂CCF₃)₂ (11.1 g, 26 mmol) and H₂SO₄ (72 mmol) were added to the reaction mixture, and the solution was heated at reflux for 2 hours. The reaction mixture was cooled to 25 °C and neutralized with saturated aqueous sodium carbonate. The aqueous layer was extracted

5

10

with methylene chloride, then the combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO₂, EtOAc-Hexanes) provided the title compound: LRMS m/z 137 (M = H⁺); IR (cm⁻¹) 3428, 1668, 1646, 1582, 1358, 1274.

10

15

5

Example 2054-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-pyridyl)pyrido[2,3-d]pyrimidine trihydrochloride salt

20

Following the procedure of Example 204, 5-dimethylaminopyridine-2-ethanone was reacted with bromobenzaldehyde, malononitrile, and ammonium acetate to give the title compound. The residue was triturated with excess HCl/ether, the volatiles were removed under reduced pressure, and the title compound was dried under high vacuum: LRMS m/z 421/423. IR (cm⁻¹) 3245, 1664, 1545, 1395.

25

The 5-dimethylaminopyridine-2-carboxaldehyde starting material was prepared as follows:

30

205a. 3-N,N-dimethylaminopyridine

35

A solution of 3-aminopyridine (9.4 g, 0.10 mol) in a 1:1 mixture of formic acid (96%) and formaldehyde (37% aqueous solution) was heated at reflux for 18 hours. The volatiles were removed under reduced pressure and the residue was neutralized with saturated aqueous NaHCO_3 . The aqueous layer was extracted with CH_2Cl_2 , then the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (SiO₂, EtOAc-Hexanes) provided the title compound: (11.1 g, 91%), LRMS m/z 123 (M + H⁺).

40

25

205b. 2-bromo-5-N,N-dimethylaminopyridine

45

A solution of 3-N,N-dimethylaminopyridine (5.88 g, 48.1 mmol) in 150 mL of CH_2Cl_2 at 0 °C was treated with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (20.7 g, 50 mmol) in several portions over 30 minutes. After 2 hours at 0 °C the reaction

50

5

mixture was concentrated, and the desired 2-bromo-5-N,N-dimethylaminopyridine was isolated following flash chromatography (16.5 g, 82%): LRMS m/z 201/203.

10

204c. 5-N,N-dimethylaminopyridine-2-ethanone

15

Following the procedure of Example 203b, 2-bromo-5-N,N-dimethylaminopyridine, except converting the compound to the trihydrochloride salt by treatment with HCl/ether, was converted to the title compound: LRMS m/z 165; IR (cm^{-1}) 3480, 1666, 1581, 1368, 1272.

20

10 Example 206

25

4-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-pyrazinyl)-
pyrido[2,3-d]pyrimidine hydrochloride

30

Following the procedure of Example 204, 5-dimethylaminopyrazine-2-ethanone was reacted with bromobenzaldehyde, malononitrile, and ammonium acetate to give the title compound. The residue was triturated with excess HCl/ether, the volatiles were removed under reduced pressure, and the title compound was dried under high vacuum: LRMS m/z 422/424. IR (cm^{-1}) 3310, 1630, 1525, 1444, 1375.

35

The 5-dimethylaminopyrazine-2-carboxaldehyde starting material was prepared as follows:

40

206a. 5-dimethylaminopyrazine-2-ethanone

45

A solution of 5-hydroxypyrazine-2-carboxylic acid (4.0 g, 28.5 mmol) in 50 mL of thionyl chloride and 0.1 mL of DMF was heated at reflux for 8 hours. The volatiles were removed under reduced pressure, and the residue was dissolved in 20 mL of toluene. This solution was added to a solution of dimethyl malonate (4.75 g, 36 mmol), MgCl_2 (2.09 g, 22 mmol) and triethyl amine (7.08 g, 70 mmol) in 100 mL of toluene. The reaction mixture was stirred for 1 hour at 25 °C, quenched by addition of water, and the product was extracted with methylene chloride. The solvent was removed, the crude intermediate was dissolved in 25 mL of a 25:1

50

5

10

15

mixture of DMSO and water, and the resulting solution was warmed at 150 °C for 2 hours. The reaction was quenched by addition of water, and the product was extracted with methylene chloride to provide 2-acetyl-5-chloropyrazine (LRMS m/z 156). This intermediate was treated with aqueous dimethylamine at room temperature for 30 minutes to afford 5-dimethylaminopyrazine-2-ethanone (LRMS m/z 166): LRMS m/z 422/424; IR (cm^{-1}) 3310, 1630, 1525, 1444, 1375.

20

Example 207

4-amino-5-(3-bromophenyl)-7-(2-oxobenzoxazolin-6-yl)pyrido[2,3-d]pyrimidine

25

Following the procedure of Example 204, 2-oxobenzoxazolin-6-ethanone was reacted with bromobenzaldehyde, malononitrile, and ammonium acetate to prepare the title compound: LRMS m/z 434/436; IR (cm^{-1}) 3095, 1760, 1579, 1481, 1350.

15 The 2-oxobenzoxazolin-5-ethanone starting material was prepared as follows:

30

207a. 2-oxobenzoxazolin-6-ethanone

35

DMF (9 mL) was added dropwise to AlCl₃ (58.7 g, 440 mmol) over 20 minutes and the resulting suspension was stirred 15 minutes at 25 °C. Acetic anhydride (7.14 g, 70 mmol) and 2-benzoxazolinone (6.0 g, 44 mmol) were added and the reaction mixture was warmed at 80 °C and stirred for 4 hours. The mixture was cooled to 25 °C and poured into ice/H₂O. The resulting precipitate was collected by filtration and dried under vacuum to provide the title compound (6.4 g, 81%, LRMS m/z 177).

40

25

Example 208

45

4-amino-5-(3-bromophenyl)-7-(1-methyl-2-oxobenzoxazolin-6-yl)-pyrido[2,3-d]pyrimidine

50

5

10

15

25

40

50

Following the procedure of Example 204, 1-methyl-2-oxobenzoxazolin-5-ethanone was reacted with bromobenzaldehyde, malononitrile, and ammonium acetate to prepare the title compound: LRMS m/z 448/450; IR (cm^{-1}) 3440, 1782, 1605, 1458, 1350.

5 The 1-methyl-2-oxobenzoxazolin-5-ethanone starting material was prepared as follows:

10 A solution of 2-oxobenzoxazolin-5-ethanone (from Example 206a, 2.50 g, 14.1 mmol) in 20 mL of a 4:1 mixture of THF and DMF at 0 °C was treated with NaH (60 % dispersion, 0.8 g, 20 mmol) and the mixture was stirred 20 minutes at 0 °C. Methyl iodide (3.97 g, 28 mmol) was added and the reaction mixture was warmed to 25 °C and stirred for 15 minutes. Saturated aqueous NaHCO_3 was added and the aqueous layer was extracted with CH_2Cl_2 . The desired product (2.55 g, 94%, 15 LRMS m/z 191), was isolated following flash chromatography (SiO_2 , EtOAc- CH_2Cl_2).

30 Example 209

20 4-amino-5-((5-chloro-2-(3-methoxyphenyl)phenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine

35 The title compound was prepared from the compound of Example 173 by reaction with 3-methoxyphenylboronic acid, $\text{Pd}(\text{PPh}_3)_4$, and aqueous sodium carbonate under Suzuki reaction conditions. IR (KBr) 3550-3250, 3240-2760, 1580, 1560, 1540, 1350; H. Rcs. MS m/z 496.1902 ($\text{M}+\text{H}$)⁺.

25

45 Example 210

4-amino-5-((2-bromophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine

Following the procedures of Example 157, except substituting 1-(4-dimethylaminophenyl)-ethanone for the R¹ reagent and 2-(2-bromophenyl)-

55

5

10

15

20

25

30

35

40

45

50

acetaldehyde for the R¹ reagent of Example 157, the title compound was prepared as shown in Table 6.

Table 6

Ex. No.	Name	R ¹ Reagent (for 7-position)	R ² Reagent (for 5-position)	Analytical Data
210	4-amino-5-((2-bromophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	2-(2-bromophenyl)-acetaldehyde	IR (KBr); MS m/z 434,436 (M+H) ⁺ .

5

10

15

20

25

30

35

40

45

50

Example 2114-amino-5-((2-thiophene-2-yl)phenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine

The title compound was prepared from the compound of Example 173 by reaction with 2-thiopheneboronic acid, Pd(PPh₃)₄, and aqueous sodium carbonate under Suzuki reaction conditions. IR (KBr) 3640-3240, 3240-2800, 1580, 1560, 1540, 1350; H. Res. MS m/z 466.2070 (M+H)⁺.

Example 2124-amino-5-((2-thiophene-3-yl)phenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine

The title compound was prepared from the compound of Example 173 by reaction with 3-thiopheneboronic acid, Pd(PPh₃)₄, and aqueous sodium carbonate under Suzuki reaction conditions. IR (KBr) 3640-3240, 3240-2800, 1580, 1560, 1540, 1350; H. Res. MS m/z 466.2057 (M+H)⁺.

5

Examples 213-222

10

Following the procedures of Example 1, except substituting the appropriate reagents for R⁴ and R³ as indicated in Table 7 below, compounds of Examples 212-222 were prepared.

15

5

Table 7Examples 213-222

20

25

30

35

40

45

50

Ex. No.	Name	R ⁴ Reagent (for 7-position)	R ³ Reagent (for 5-position)	Analytical Data
213	4-amino-5-(3-bromophenyl)-7-(4-(N-formyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(N-formyl-N-(2-methoxyethyl)amino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3490, 1689, 1120, 800 cm ⁻¹ ; MS m/z 478/480 (M+H) ⁺ .
214	4-amino-5-(3-bromophenyl)-7-(4-(N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;	* 1-(4-(N-(2-methoxyethyl)amino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3330, 2925, 1675, 800 cm ⁻¹ ; MS m/z 451/453 (M+H) ⁺ .
215	4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-((2-dimethylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(N-methyl-N-((2-dimethylamino)ethyl)amino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3440, 1600, 1160, 810 cm ⁻¹ ; MS m/z 477/479 (M+H) ⁺ .

55

5

10

15

20

25

30

35

40

45

50

	216	4-amino-5-(3-bromophenyl)-7-(4-(2-methoxyacetylamino)ethylamino)phenyl-ethanone pyrido[2,3-d]pyrimidine;	** 1-(4-(2-methoxyacetylamino)ethylamino)phenyl-ethanone	3-bromo-benzaldehyde	IR (KBr) 3480, 1520, 710 cm ⁻¹ ; MS m/z 464,466 (M+H) ⁺ .
	217	4-amino-5-(3-bromophenyl)-7-((4-formylamino)phenyl)pyrido[2,3-d]pyrimidine;	*** 1-(4-(formylamino)phenyl-ethanone	3-bromo-benzaldehyde	IR (KBr) 3475, 1690, 1355, 800 cm ⁻¹ ; MS m/z 420/422 (M+H) ⁺ .
	218	4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)acetylamino)phenyl)pyrido[2,3-d]pyrimidine;	**** 1-(4-(2-(dimethylamino)acetylamino)phenyl-ethanone	3-bromo-benzaldehyde	IR (KBr) 3452, 1605, 1250, 590 cm ⁻¹ ; MS m/z 477/479 (M+H) ⁺ .
	219	4-amino-5-(3-bromophenyl)-7-(4-(2-oxo-3-oxazolidinyl)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(2-oxo-3-oxazolidinyl)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3480, 1750, 1400, 700 cm ⁻¹ ; MS m/z 462/464 (M+H) ⁺ .
	220	4-amino-5-(3-bromophenyl)-7-(6-(2-propyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine trihydrochloride	1-(6-(2-propyl)-3-pyridinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3474, 3098, 1636, 1566, 1499, 1352, 1282 cm ⁻¹ ; MS m/z 393 (M+H) ⁺ .

55

5

10

15

20

25

30

221	4-amino-5-(3-bromophenyl)-7-(3-methyl-4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine dihydrochloride	1-(3-methyl-4-pyrrolidinylphenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3440, 1640, 1607, 1586, 1370 cm ⁻¹ ; MS m/z 433 (M+H) ⁺ .
222	4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridinyl)-pyrido[2,3-d]pyrimidine trihydrochloride	1-(6-imidazolyl-3-pyridinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3028, 1641, 1607, 1595, 1375cm ⁻¹ ; MS m/z 417 (M+H) ⁺ .

*prepared by deformylation of Example 213 with dilute HCl in methanol.

**prepared by acylation of Example 213 with 2-methoxyacetyl chloride/pyridine.

***prepared by formylation of the 7-(3-bromophenyl)-2-cyano-5-(4-aminophenyl)pyridine-2-amine intermediate.

****prepared by acylation of Example 213 with the 2-(dimethylamino)acetyl chloride.

Examples 223-225

35

Following the procedures of Example 157, except substituting the appropriate reagents for the R⁴ and R³ reagents of Example 157 as indicated in Table 8 below, compounds of Examples 223-225 were prepared.

40

Table 8Examples 223-225

15

45

Ex. No.	Name	R ⁴ Reagent (for 7-position)	R ³ Reagent (for 5-position)	Analytical Data
------------	------	--	--	-----------------

50

5

10

15

20

25

30

35

40

45

50

55

	223	4-amino-5-phenylmethyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine	1-(4-diethylaminophenyl)-ethanone	2-phenyl-acetaldehyde	IR (KBr) 3450,3380,2850- 3200,1605,1580,15 60,1540; H. Res. MS m/z 384.2176 (M+H) ⁺ .
	224	4-amino-5-(2-(3-aminopropynyl)phenylmethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine	1-(4-diethylaminophenyl)-ethanone	* from Example 170, palladium coupling with 3-aminopropyne	IR (KBr) 2400- 3450,2050,2120,16 50,1605,1540; MS m/z 437 (M+H) ⁺ .
	225	4-amino-5-(1-(2-bromophenyl)ethyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine	1-(4-dimethylaminophenyl)-ethanone	2-(2-bromophenyl)-propionaldehyde	IR (KBr) 3520,3250- 3500,2850- 3150,1605,1580,15 60,1540; H. Res. MS m/z 448.1137 (M+H) ⁺ .

*prepared from the compound of Example 170 by reaction with propargylamine, CuI and Pd(PPh₃)₄ under Suzuki reaction conditions.

Examples 226-228

Following the procedures of Example 1, except substituting the appropriate reagents for R⁴ and R⁵ as indicated in Table 9 below, compounds of Examples 226-228 were prepared.

5

Table 9
Examples 226-228

10

	Ex. No.	Name	R ⁴ Reagent (for 7- position)	R ⁵ Reagent (for 5- position)	Analytical Data
15	226	4-amino-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine	1-(4-bromophenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3456, 3053, 16600, 1556 cm ⁻¹ ; MS m/z 420 (M+H) ⁺ .
20	227	4-amino-5-(2-furanyl)-7-(4-(N-morpholinyl)phenyl)pyrido[2,3-d]pyrimidine	1-(4-(N-morpholinyl)phenyl)ethanone	furan-2-carboxaldehyde	IR (KBr) 3460, 1600, 1580, 1457 cm ⁻¹ ; MS m/z 374 (M+H) ⁺ .
25	228	4-amino-5-(3-bromophenyl)-7-(2-dimethylamino-5-pyrimidinyl)pyrido[2,3-d]pyrimidine	1-(5-(2-(dimethylamino)pyrimidinyl))ethane	3-bromo-benzaldehyde	IR (KBr) 3442, 1640, 1604, 1577, 1536, 1408, 1367, 1348 cm ⁻¹ ; MS m/z 422 (M+H) ⁺ .

40

5

Example 2294-amino-5-(3-bromophenyl)-7-(4-(ureido)phenyl)pyrido[2,3-d]pyrimidine

45

A solution of 4-amino-5-(3-bromophenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine (Example 71, 310 mg, 0.79 mmol) in 2 mL of acetic acid was treated with sodium cyanate (56 mg, 0.87 mmol), and the reaction mixture was stirred for 30 minutes at 25 °C. The solution was concentrated and the residue was suspended in aqueous

50

5

NaHCO₃. The crude product was collected by filtration, then purified by flash chromatography. The product was dissolved in methanol and treated with excess 2M aqueous HCl to provide the hydrochloride salt: LRMS m/z 435/437, IR (cm⁻¹) 3442, 10 2212, 3186, 3059, 1681, 1582, 1525, 1358.

15

5

Example 230

15

4-amino-5-(1-phenylmethyl-3-piperidinyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine

20

Following the procedures of Example 157, except substituting 1-(4-diethylamino-phenyl)-ethanone for the R⁴ reagent and 1-phenylmethylpiperidine-3-carboxaldehyde (prepared as described by Gilligan et al., J. Med. Chem., 35:4344-4361 (1992)) for the R³ reagent thereof, the title compound was prepared. The treatment with aqueous HCl was omitted, and the free base was obtained. IR (KBr) 3440, 3100-2800-1640, 1605, 1595, 25 1535 cm⁻¹; MS m/z 467 (M+H)⁺; mp 218-220 °C.

30

Examples 231-243

35

Following the procedures of Example 1, except substituting the appropriate reagents for R⁴ and R³ as indicated in Table 10 below, compounds of Examples 230-243 were prepared. In some cases, the treatment with aqueous HCl was omitted, and the free bases were obtained. Some compounds were isolated as the TFA salt following purification via high pressure liquid chromatography (HPLC).

40

45

50

5

Table 10
Examples 231-243

10

	Ex. No.	Name	R ¹ Reagent (for 7-position)	R ² Reagent (for 5-position)	Analytical Data
15	231	4-amino-5-(3-bromophenyl)-7-(6-(3-methyl-5-isoxazolyl))-3-pyridinyl)pyrido[2,3-d]pyrimidine;	1-(6-(3-methyl-5-isoxazolyl))-3-pyridinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3484, 1635, 1574, 1562, 1352 cm ⁻¹ ; MS m/z 459 (M+H) ⁺ .
20	232	4-amino-5-(3-bromophenyl)-7-(6-chloro-3-pyridinyl)pyrido[2,3-d]pyrimidine;	1-(6-chloro-3-pyridinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3478, 1608, 1574, 1542 cm ⁻¹ ; MS m/z 414 (M+H) ⁺ .
25	233	4-amino-5-(3-bromophenyl)-7-(6-methoxy-3-pyridinyl)pyrido[2,3-d]pyrimidine;	1-(6-methoxy-3-pyridinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3484, 1635, 1560, 1348 cm ⁻¹ ; MS m/z 409 (M+H) ⁺ .
30	234	4-amino-5-(3-bromophenyl)-7-(6-(1,2,4-triazol-4-yl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;	1-(6-(1,2,4-triazol-4-yl))-3-pyridinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3494, 1612, 1579, 1467, 1359, 1271, 1233 cm ⁻¹ ; MS m/z 445 (M+H) ⁺ .
35					
40					
45					

50

5

10

15

20

25

30

35

40

45

50

55

	235	4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;	1-(2-morpholinyl-5-pyrimidinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3434, 1637, 1608, 1585, 1335, cm ⁻¹ ; MS m/z 463 (M+H) ⁺ .
	236	4-amino-5-(2-thiazolyl)-7-(4-pyrrolidinylphenyl)-pyrido[2,3-d]pyrimidine;	1-(4-pyrrolidinylphenyl)-ethanone	2-thiazole-carboxaldehyde	IR (KBr) 3400, 1637, 1608, 1532, cm ⁻¹ ; MS m/z 376 (M+H) ⁺ .
	237	4-amino-5-(3-bromophenyl)-7-(6-pyrazolyl-3-pyridinyl)-pyrido[2,3-d]pyrimidine;	1-(6-pyrazolyl-3-pyridinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3474, 1580, 1562, 1492, 1395, cm ⁻¹ ; MS m/z 444 (M+H) ⁺ .
	238	4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-ureido)phenyl)-pyrido[2,3-d]pyrimidine;	1-(4-(1-methyl-ureido)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3400, 1665, 1350 cm ⁻¹ ; MS m/z 450 (M+H) ⁺
	239	4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-pyrimidinyl)amino)phenyl)-pyrido[2,3-d]pyrimidine;	1-(4-(N-methyl-N-(2-pyrimidinyl)amino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3475, 1578, 1553, 1482, 1396, cm ⁻¹ ; MS m/z 484 (M+H) ⁺ .

5

	240	4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-methylamino)phenyl)-pyrido[2,3-d]pyrimidine; *	1-(3-fluoro-4-(N-methylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3448, 1600, 1525, 1476, cm ⁻¹ ; MS m/z 484 (M+H) ⁺ .
10	241	4-formylamino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-methylamino)phenyl)-pyrido[2,3-d]pyrimidine; *	1-(3-fluoro-4-(N-methylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3465, 1607, 1546, 1350, cm ⁻¹ ; MS m/z 481 (M+H) ⁺ .
15	242	4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-methylsulfonylamino)phenyl)pyrido[2,3-d]pyrimidine;	1-(4-(N-methyl-N-methylsulfonylamino)phenyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3470, 1650, 1570, 1338, cm ⁻¹ ; MS m/z 484 (M+H) ⁺ .
20	243	4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methylsulfonylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine;	1-(6-(N-methyl-N-methylsulfonylamino)-3-pyridinyl)-ethanone	3-bromo-benzaldehyde	IR (KBr) 3460, 1680, 1580, 1330 cm ⁻¹ ; MS m/z 485 (M+H) ⁺ .
25					
30					
35					
40					

* separated by chromatography from the same reaction mixture; formylation occurs during the cyclization step

45

50

5

Example 2444-amino-5-(3-bromophenyl)-7-(1-methyl-5-indolinyl)pyrido[2,3-d]pyrimidine dihydrochloride

10

5 A sample of 4-(3-bromophenyl)-3-cyano-6-(1-methyl-5-indolinyl)pyridine-2-amine was heated at reflux in formamide. The reaction was monitored by TLC, and
15 when the reaction was complete the mixture was cooled to room temperature. The product was allowed to precipitate, then recovered by filtration and washed with water. Additional product was extracted from the filtrate. The product was purified
20 by column chromatography eluting with 10% MeOH/CH₂Cl₂ and converted to the hydrochloride salt by treatment with ether/HCl. The salt was isolated and dried under vacuum to give the title compound. LRMS m/z 432/434; IR (cm⁻¹) 3500,
25 3400, 3300, 3200-2800, 1610, 1580, 1560, 1540.

25 The 4-(3-bromophenyl)-3-cyano-6-(1-methyl-5-indolinyl)pyridine-2-amine
15 starting material was prepared as follows:

30 244a. 5-bromo-1-methylindoline

30 Acetic acid (60 mL) was added to a mixture of 5-bromo-1-methylindole (10 g, 47.6 mmol) and sodium cyanoborohydride (8 g). After one hour at 15 °C, the
20 reaction was basified with aqueous NaOH and extracted with toluene. The organic
35 phase was dried over MgSO₄, and concentrated to a powder under vacuum. This material was purified by flash chromatography to give the title compound, 8.62 g (82 %): MS 212, 214 [M+H]⁺.

40 244b. 5-acetyl-1-methylindoline

45 A mixture of 5-bromo-1-methylindoline (8.6 g, 40.7 mmol), trimethylsilylacetylene (12 mL), palladium bis-triphenylphosphine dichloride (600 mg), CuI (620 mg) and triethylamine (16 mL) in acetonitrile (20 mL) was heated at 75 °C for 3 days, then cooled and concentrated in vacuo. The residue was dissolved
30 in 120 mL of 1:1 ethyl acetate/hexane, and the solids were removed by filtration.

50

5

10

The solvent was removed and a sample of the residue (5 g) was dissolved in 90% aqueous acetone (44 mL). To this solution was added sulfuric acid (2.2 g), and Hg(OCOCF₃)₂ (9 g). The reaction was heated at reflux for 20 minutes, cooled, made basic with aqueous sodium hydroxide and extracted with ethyl acetate. The organic layer was dried over MgSO₄, and concentrated to an oil, which was purified by flash chromatography to give 850 mg of the title compound: MS 176 [M+H]⁺.

15

20

25

30

244c. 4-(3-bromophenyl)-3-cyano-6-(1-methyl-5-indolinyl)pyridine-2-amine

Prepared by condensation of 1',1'-dicyano-3-bromostyrene (prepared by condensation of 3-bromobenzaldehyde with malononitrile in ethanol in the presence of a catalytic amount of glycine) and the 5-acetyl-1-methylindoline (the R⁴ reagent) with ammonium acetate in ethanol. After 3.5 hours, the mixture was cooled, and the solvent was removed. The residue was purified by flash chromatography, eluting with methylene chloride, to give the title compound (588 mg, 30% yield; MS m/z 394 (M+H)⁺).

Example 245

4-amino-5-(3-bromophenyl)-7-(1-methyl-5-benzimidazolyl)pyrido[2,3-d]pyrimidine tetrahydrochloride

35

40

45

The title compound was prepared according to the procedure of Example 1, except substituting 1-methyl-5-acetyl-benzimidazole (prepared according to the procedure of D. J. Evans et. al., J. Chem. Soc. Perkin Trans. II, 1978, 865) for the 4-dimethylaminobenzaldehyde (the R³ reagent) therein. IR (KBr) 3650-3230, 3230-2000, 1635, 1605, 1590, 1555, 1365 cm⁻¹; MS m/z 431/433, 431.0605 (M+H)⁺.

Example 246

4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine tetrahydrochloride

50

55

5

10

15

20

25

30

35

40

45

50

246a. 6-(1-butoxyethenyl)-3-chloropyridazine

To a solution of 20 g (200 mmol) of butyl vinyl ether in 80 mL of THF at -78 °C was added 130 mL of a 1.7 M solution of t-butyl lithium in pentane over about 20 minutes. The yellow suspension was stirred while allowing to warm to 0 °C. THF (150 mL) was added, and the mixture cooled to -78 °C and a solution of 23 mL (200 mmol) of trimethyl borate in 50 mL of THF was added. The reaction was warmed to 20 °C, 20 mL of methanol was added, and the solution concentrated in vacuo. The residue was diluted with 400 mL of dioxane, and 20.9 g (140 mmol) of 3,6-dichloropyridazine, 2.31 g of Pd(PPh₃)₄, and 200 mL of 2 M aqueous sodium carbonate was added. The reaction was heated to reflux over one hour, then cooled and filtered to remove solids. The filtrate was concentrated in vacuo and partitioned between ethyl acetate and 1 M sodium hydroxide. The organic phase was dried over Na₂SO₄, concentrated in vacuo, and purified by flash chromatography to give 6.3 g (21%) of the title compound. MS {M + }+ 213, 215.

15

246b. 1-(6-chloropyridazin-3-yl)ethanone

A mixture 6.3 g of the compound from Step 246a in 40 mL of dimethoxyethane, 10 mL of water, and 4 mL of 12 M HCl was stirred for 20 minutes, then 125 mL of water was added, and the reaction was neutralized with 12 g of NaHCO₃. The reaction was extracted with ethyl acetate, dried over Na₂SO₄, and concentrated in vacuo to give a yellow solid. 4.7 g.

246c. 1-(3-(dimethylamino)pyridazin-3-yl)ethanone (the R⁴ reagent)

A solution of 1.57 g (10 mmol) of 1-(6-chloropyridazin-3-yl)ethanone (from Step 246b) in 15 mL of dimethoxyethane was treated with 50 mmol of 40% aqueous dimethylamine. After one hour, the reaction was partitioned between CH₂Cl₂ and water. The organic phase was dried over CH₂Cl₂, and concentrated in vacuo to give the title compound.

55

5

246d. 3-acetyl-6-(dimethylamino)pyridazine

10

The title compound was prepared by condensing 1,1-dicyano-(3-(3-bromophenyl)propene (the R³ reagent) with the compound from Step 246c (the R⁴ reagent) and ammonium acetate in ethanol according to the procedure of Example 157d.

15

246e. 4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine tetrahydrochloride

20

The title compound was prepared from the compound of Step 246d according to the procedure of Example 157, except substituting formamide for the ammonium sulfate and triethyl orthoformate thereof.

Examples 247-248

Following the procedures of Example 246, except in step (c) substituting the appropriate reagents for methylamine as indicated in the Table 11A below, compounds of Examples 247-248 were prepared.

Table 11A
Examples 247-248

Ex. No.	Name	reagent of step c	Analytical Data
247	4-amino-5-(3bromophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine dihydrochloride	morpholine	IR (KBr) 3600-3200, 3000, 1630, 1605, 1590, 1550 cm ⁻¹ ; MS m/z 464/466, 464.0829 (M+H) ⁺ ;

50

5

10

15

248	4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine dihydrochloride	pyrrolidine	IR (KBr) 3600-3250, 3100-2800, 1640, 1605, 1560 cm ⁻¹ ; MS m/z 448/450, (M+H) ⁺ ;
-----	---	-------------	---

Examples 249-251

20

Following the procedures of Example 244, except in step (c) first substituting the appropriate reagent for R⁴ as indicated in Table 11B below for the R⁴ reagent of Example 244 step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the compounds of Examples 249-251 were prepared. In some cases, the hydrochloride salts were not prepared.

30

10

Table 11BExamples 249-260

35

40

45

50

Ex. No.	Name	R ⁴ Reagent (for 7-position)	Analytical Data
249	4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-pyrazinyl)pyrido[2,3-d]pyrimidine dihydrochloride	2-acetyl-5-morpholinyl-pyrazine	IR (KBr) 3478, 3058, 1562, 1542, 1378, 1306 cm ⁻¹ ; MS m/z 464/466, (M+H) ⁺ ;

5

10

15

20

25

	250	4-amino-5-(3-bromophenyl)-7-(5-(N-(2-methoxyethyl)-N-methylamino)-2-pyrazinyl)pyrido[2,3-d]pyrimidine dihydrochloride	2-acetyl-5-(N-(2-methoxyethyl)-N-methylamino)-pyrazine	IR (KBr) 3482, 3299, 3053, 1612, 1540, 1310 cm ⁻¹ ; MS m/z 466/468, (M+H) ⁺ ;
	251	4-amino-5-(3-bromophenyl)-7-(4-(morpholinylmethyl)-phenyl)pyrido[2,3-d]pyrimidine hydrochloride	1-((4-acetylphenyl)-methyl)-morpholine	IR (KBr) 3040, 1680, 1640, 1605, 1580, 1400 cm ⁻¹ ; MS m/z 466/468, (M+H) ⁺ ;

Example 2524-amino-5-(3-bromophenyl)-7-(5-(N,N-bis(2-methoxyethyl)amino)-2-pyridinyl)pyrido[2,3-d]pyrimidine trihydrochloride

30

5

Step 252a. 1-(5-bromo-2-pyridyl)ethanone, ethylene ketal

A solution of dibromopyridine (5.2 g, 21.95 mmol), tributyl(1-ethoxyvinyl)tin (9.11 g, 25.24 mmol), Pd₂(dba)₃ (0.7 g, 0.8 mmol), and (2-furyl)₃P (0.37 g, 1.6 mmol) in 50 mL of toluene/THF (5:1) was warmed at reflux for 10 hours. The reaction mixture was concentrated, and the crude product was purified by elution through a short column of silica gel. The resulting enol-ether compound, ethylene glycol (2.79 g, 45 mmol), and p-toluene sulfonic acid (0.1 g) were dissolved in 50 mL of toluene and the solution was warmed at reflux for 10 hours. The reaction mixture was quenched by the addition of saturated aqueous NaHCO₃, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was dried (Na₂SO₄), concentrated under reduced pressure, and the resulting crude product was purified by flash chromatography to provide the title compound (3.68 g, 79%).

50

5

Step 252b. 1-(5-(bis(2-methoxyethyl)amino)-2-pyridyl)ethanone

10 Following literature procedure (J. Org. Chem. 1996, 61, 720), a suspension of the compound from step 252a, bis(2-methoxyethyl)amine, t-BuONa, Pd₂(dba)₃, and BINAP
5 toluene was warmed at 80 °C for 8 hours. The reaction mixture was quenched by the addition of saturated aqueous NaHCO₃, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was concentrated and the resulting residue was dissolved in 20 mL THF/3 M HCl (4:1) and stirred for 4 h. The reaction mixture was neutralized by the addition of 2 M NaOH (aq) and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was dried, concentrated under reduced pressure, and the crude product was purified by flash chromatography to provide the title compound

15 Step 252c. 4-amino-5-(3-bromophenyl)-7-(5-(N,N-bis(2-methoxyethyl)amino)-2-pyridinyl)pyrido[2,3-d]pyrimidine trihydrochloride

20 Following the procedures of Example 244, except in step (c) first substituting the reagent from Step 252b for the R⁴ reagent of Example 244 step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the free base of the title compound was prepared. The title compound was prepared from this by treatment with HCl in ether. IR (KBr) 3440, 1635, 1605, 1580, 1360 cm⁻¹; MS m/z 466/468, (M+H)⁺.

35

Examples 253-260

40 Following the procedures of Example 244, except in step (c) first substituting the appropriate reagent for R⁴ as indicated in Table 11B below for the R⁴ reagent of Example
45 244 step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the compounds of Examples 253-260 were prepared. In some cases, the hydrochloride salts were not prepared.

50

5

	Ex. No.	Name	R ⁴ Reagent (for 7-position)	Analytical Data
10	253	4-amino-5-(3-bromophenyl)-7-(4-(imidazolylmethyl)phenyl)pyrido[2,3-d]pyrimidine trihydrochloride	1-((4-acetylphenyl)methyl)imidazole	IR (KBr) 3105, 1645, 1620, 1570, 1350 cm ⁻¹ ; MS m/z 466/468, (M+H) ⁺ ;
15	254	4-amino-5-(3-bromophenyl)-7-(5-(1-morpholinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine trihydrochloride	1-(5-morpholinyl-2-pyridyl)ethanone	IR (KBr) 3297, 3081, 1646, 1564, 1494, 1362 cm ⁻¹ ; MS m/z 463/465, (M+H) ⁺ ;
20	255	4-amino-5-(3-bromophenyl)-7-(4-((dimethylamino)methyl)phenyl)pyrido[2,3-d]pyrimidine dihydrochloride	1-(4-((dimethylamino)methyl)phenyl)ethanone	IR (KBr) 3308, 1645, 1590, 1560, 1375 cm ⁻¹ ; MS m/z 509/511, (M+H) ⁺ ;
25	256	4-amino-5-(3-bromophenyl)-7-(5-(4-hydroxy-1-piperidinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine dihydrochloride	1-(5-(4-hydroxypiperidinyl)-2-pyridyl)ethanone	IR (KBr) 3000, 1650, 1600, 1580, 1550, 1400 cm ⁻¹ ; MS m/z 477/479, (M+H) ⁺ ;
30				
35				
40				
45				
50				

5

10

15

20

25

30

35

40

45

50

55

	257	4-amino-5-(3-bromophenyl)-7-(5-(N-formyl-N-methylamino)-2-pyridinyl)pyrido[2,3-d]pyrimidine dihydrochloride	5-acetyl-2-pyridinemethanamine	IR (KBr) 3477, 3060, 1678, 1638, 1566, 1495, 1319 cm ⁻¹ ; MS m/z 435/437, (M+H) ⁺ ;
	258	4-amino-5-(3-bromophenyl)-7-(5-(2-propenyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine	2-acetyl-5-(2-propenyl)-pyridine	IR (KBr) 3085, 1562, 1485, 1357 cm ⁻¹ ; MS m/z 418/420, (M+H) ⁺ ;
	259	4-amino-5-(3-bromophenyl)-7-(3-(2-methoxyethyl)-2-oxo-6-benzoxazolyl)pyrido[2,3-d]pyrimidine hydrochloride	6-acetyl-3-(2-methoxyethyl)-benzoxazol-2-one	IR (KBr) 3440, 1770, 1625, 1605, 1580, 1360 cm ⁻¹ ; MS m/z 492/494, (M+H) ⁺ ;
	260	4-amino-5-(3-bromophenyl)-7-(4-(1-(N-formylamino)-ethyl)phenyl)pyrido[2,3-d]pyrimidine	N-(1-(4-acetyl-phenyl)ethyl)-formamide	IR (KBr) 3283, 3054, 1678, 1631, 1547, 1352 cm ⁻¹ ; MS m/z 448/450, (M+H) ⁺ ;

* Prepared as in Ex. 252b, except substituting morpholine for the bis(2-methoxyethyl)amine thereof.

** Prepared as in Ex. 252b, except substituting 4-hydroxypiperidine for the bis(2-methoxyethyl)amine thereof.

5

5

Example 2614-amino-5-(3-pyridyl)-7-(4-dimethylamino)phenylpyrido[2,3-d]pyrimidine

10

The compound was prepared by using the method generally described above in Scheme 3 and the associated examples using 1-(4-dimethylaminophenyl)ethanone as the R⁴ reagent (7-position) and nicotinaldehyde as the R³ reagent (5-position). IR (cm-1) 3305.8, 2922, 1606, 1578, 1535, 1360. MS (M+II) 342.

15

Example 2624-(methylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine

20

hydrochloride

The title compound was prepared by using the method described in Example 200, except substituting methylamine for the 2-(dimethylamino)ethylamine thereof. MS (M+H), 478 (1Br); IR (cm-1) 3455, 3047, 2959, 1580, 1351, 1234.

25

15

Example 2634-(2-methoxyethylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine hydrochloride

30

The title compound was prepared by using the method described in Example 200, except substituting 2-methoxyethylamine for the 2-(dimethylamino)ethylamine thereof.

MS (M+H), 522 (1Br); IR (cm-1) 3415, 2920, 1569, 1321, 1234.

35

Example 2644-amino-5-(3-bromophenyl)-7-(4-(1-methyl-2-imidazolyl)phenyl)pyrido[2,3-d]pyrimidine trihydrochloride

40

25

Step 264a. 1-(4-(1-Methylimidazol-2-yl)phenyl)ethanone

45

A solution of N-methyl imidazole (0.90 g, 11.0 mmol) in 12 mL of THF at -78 °C was treated with n-BuLi (7.5 mL, 1.6 M solution in hexanes, 12.0 mmol) for 0.5 hours at -78 °C. Next, ZnCl₂ (20 mL, 1.0 M solution in Et₂O, 20 mmol) was added, and the

30 solution was warmed to 25°C. To this solution was added Pd(PPh₃)₄ (70 mg, 0.06 mmol)

50

5

10

15

20

25

30

35

45

50

followed by 4-iodoacetophenone ethylene acetal (prepared from iodoacetophenone and ethylene glycol in the presence of an acid catalyst by standard procedures), and the reaction mixture was heated at reflux for 4 hours. The solution was then cooled to 25 °C and quenched by the addition of saturated aqueous NaHCO₃ (10 mL). The aqueous layer was extracted with CH₂Cl₂, and the combined organic layer was concentrated under reduced pressure. The residue was dissolved in 30 mL of THF, 15 mL of 3 M aqueous HCl was added, and the mixture was stirred for 2 hours at 25 °C. The solution was neutralized by the addition of saturated aqueous NaHCO₃, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was dried (MgSO₄) then concentrated under reduced pressure. The crude product was purified by flash chromatography to provide the title compound (0.89 g, 64%).

Step 264b. 4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-2-imidazolyl)phenyl)pyrido[2,3-d]pyrimidine trihydrochloride

15 Following the procedures of Example 244, except in step (c) first substituting the R⁴ reagent from Step 264a for the R⁴ reagent of Example 244 step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the title compound was prepared. MS (M+H) 458 (1Br); IR (cm⁻¹) 3051, 2948, 1577, 1474, 1354.

20

Examples 265-267

Following the procedures of Example 244, except in step (c) first substituting the appropriate reagent for R⁴ as indicated in the Table below for the R⁴ reagent of Example 244 step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the compounds of Examples 264-285 were prepared. In Ex. 266, the hydrochloride salt was not prepared.

5

	Ex. No.	Name	R ⁴ Reagent (for 7-position)	Analytical Data
10	265	4-amino-5-(3-bromophenyl)-7-(4-(aminomethyl)phenyl)pyrido[2,3-d]pyrimidine	1-(4-(aminomethyl)phenyl)ethanone	MS (M+H), 460; IR (cm-1) 3024, 2933, 1550, 1493, 1328
15	266	4-amino-5-(3-bromophenyl)-7-(2-bromo-4-(dimethylamino)phenyl)ethanone	1-(2-bromo-4-(dimethylamino)phenyl)ethanone	MS (M+H), 500 (2 Br); IR (cm-1) 3049, 2949, 1536, 1468, 1320
20	267	4-amino-5-(3-bromophenyl)-7-(4-(dimethylaminoethyl)phenyl)pyrido[2,3-d]pyrimidine	1-(4-(dimethylaminoethyl)phenyl)ethanone	MS (M+H), 448 (1 Br); IR (cm-1) 3420, 3000, 2980, 1635, 1610, 1590, 1435, 1415
25				
30				

Example 2684-amino-5-(3-bromophenyl)-7-(4-(3-(dimethylamino)propynyl)phenyl)pyrido[2,3-d]pyrimidine

35

5 A suspension of the compound of Example 63 (0.80 g, 1.59 mmol), PdCl₂(PPh₃)₂, CuI, and 3-dimethylaminoprop-1-yne in 20 mL of DMF/TEA (4:1) was heated at 50 °C for 3 hours. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography to provide the title compound (0.50 g, 68 %). MS (M+H), 459 (1Br); IR (cm-1) 3027, 2964, 1513, 1470, 1360.

10

45

50

5

Examples 269-271

10

Following the procedures of Example 268, except substituting the reagent compound shown in the table below for the 3-dimethylaminoprop-1-yne of Example 268, the compounds shown in the table below were prepared.

5

Ex. No.	Name	Reagent	Analytical Data
269	4-amino-5-(3-bromophenyl)-7-(4-(3-amino-3-methylbutynyl)phenyl)pyrido[2,3-d]pyrimidine	1,1-dimethyl-propargyl amine	MS (M+H), 459 (1Br); IR (cm-1) 3041, 2967, 1562, 1484, 1319
270	4-amino-5-(3-bromophenyl)-7-(4-dimethylphosphonatophenyl)pyrido[2,3-d]pyrimidine	dimethyl phosphite	MS (M+H), 486 (1Br); IR (cm-1) 3105, 2912, 1625, 1437, 1350
271	4-amino-5-(3-bromophenyl)-7-(4-(3-(methoxypropynyl)pyrido[2,3-d]pyrimidine	methyl propargyl ether	MS (M+H), 446 (1Br); IR (cm-1) 3053, 2929, 1560, 1484, 1352

40

Example 2724-amino-5-(3-bromophenyl)-7-(4-carboxyphenyl)pyrido[2,3-d]pyrimidine

45

A solution of 4-amino-5-(3-bromophenyl)-7-(4-cyanophenyl)pyrido[2,3-

10 d]pyrimidine (the compound of Example 37, (0.47 g, 1.17 mmol) in 15 mL of 6 M HCl (aqueous) was heated at 60 °C for 8 hours. The mixture was lyophilized and the crude product was purified by flash chromatography to provide the title compound (0.14 g, 28%). MS (M+H), 422 (1Br); IR (cm-1) 3064, 2628, 1692, 1403, 1273.

50

5

Example 273

10

4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazinyl)pyrido[2,3-d]pyrimidine

15

Step 273a. 7-acetyl-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one

A solution of 2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (9.8 g, 65.27 mmol, Aldrich) in 120 mL of THF/MeOH (5:1) was treated with 0.4 mL of concentrated HCl (aqueous) followed by N-bromosuccinimide (17.8 g, 100 mmol) in several portions over 10 minutes. After 12 hours at 25 °C the reaction mixture was quenched by the addition of saturated aqueous NaHSO₃. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layer was dried (Na₂SO₄), concentrated under reduced pressure, and purified by flash chromatography to provide 7-bromo-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (8.4 g, 56%). A mixture of 7-bromo-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (3.2 g, 14 mmol), tributyl(1-ethoxyvinyl)tin (6.1 g, 17 mmol), Pd₂(dba)₃ (0.5 g, 0.56 mmol), and (2-furyl)₃P (0.3 g, 1.2 mmol) in 30 mL of toluene/THF (5:1) was warmed at reflux for 10 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in 50 mL of THF. 15 mL of 4 M HCl (aqueous) was added, and the mixture was stirred for 4 hours at 25 °C. The solution was neutralized by the addition of NaHCO₃ (aqueous), and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was dried (Na₂SO₄), concentrated, and the crude product was purified by flash chromatography to provide 7-acetyl-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (2.37 g, 88%). MS (M+H)⁺, 463 (1 Br); IR (cm⁻¹) 3400, 3200-2800, 1700, 1640, 1605, 1590, 1395, 1380, 1345.

20

25

Step 273b. 7-acetyl-4-methyl-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one

25

The compound from step 273 a was treated with methyl iodide and NaH in 1:1 THF/DMF for 6 hours at 0 °C to 25 °C. The reaction was quenched with aqueous sodium

50

5

bicarbonate solution. the mixture was extracted with dichloromethane, and the residue was purified by chromatography to give the title compound. MS (M+H), 407.

10

Step 273c. 4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazinyl)pyrido[2,3-d]pyrimidine

15 Following the procedure of Example 244 Step c, except first substituting 7-acetyl-4-methyl-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (the R⁴ reagent) from Step 273b for the R³ reagent of Example 244 Step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol
20 solvent in Example 244 step c, the title compound was prepared. MS (M+H), 463 (1 Br); IR (cm⁻¹) 3400, 3200-2800, 1700, 1640, 1605, 1590, 1395, 1380, 1345.

Example 274

25 4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)ethyl)-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

30 Step 274a. 7-acetyl-4-dimethylaminoethyl -2H-pvrido[3,2-b]-1,4-oxazin-3(4H)-one

The compound from Example 273 Step a was treated with 2-chloro-(N,N-dimethyl)ethylamine HCl and K₂CO₃ in aqueous acetone at reflux. The mixture was diluted with water and extracted with dichloromethane, and the residue was purified by chromatography to give the title compound.

40 Step 274b. 4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)ethyl)-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

25 Following the procedures of Example 244 Step c, except in step c first substituting 7-acetyl-4-dimethylaminoethyl -2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (the R⁴ reagent, from Step 273b) for the R³ reagent of Example 244 Step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the title compound was prepared. MS (M+H),
45 519 (1 Br); IR (cm⁻¹) 3440, 1685, 1630, 1605, 1580, 1395

50

5

Example 275

10 4-amino-5-(3-bromophenyl)-7-(2,3-dihydro-3-(dimethylaminoethyl)-2-oxobenzoxazol-6-vl)pyrido[2,3-d]pyrimidine

5

Step 275a. 6-acetyl-2-benzoxazolinone

15 Following the procedures of Example 273 Step a, except substituting 2-benzoxazolinone (Aldrich) for the 2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one thereof, the title compound was prepared.

10

Step 275b. 6-acetyl-3-(dimethylaminoethyl)-2-benzoxazolinone

20 The compound from Example 275 Step a was treated with 2-chloro-(N,N-dimethyl)ethylamine HCl and K₂CO₃ in aqueous acetone at reflux. The mixture was
25 diluted with water and extracted with dichloromethane, and the residue was purified by
15 chromatography to give the title compound.

30 Step 275c. 4-amino-5-(3-bromophenyl)-7-(2,3-dihydro-3-(dimethylaminoethyl)-2-oxobenzoxazol-6-vl)pyrido[2,3-d]pyrimidine

35 Following the procedures of Example 244 Step c, except in step c first substituting
20 the compound from Step 275a for the R⁴ reagent of Example 244 Step c, and secondly
performing the condensation with ammonium acetate substituting dichloroethane as the
solvent in place of the ethanol solvent in Example 244 step c, the title compound was
prepared. MS (M+H), 506 (1 Br); IR (cm⁻¹) 3400, 3050, 1630, 1610, 1360.

40

45

50

5

Example 276

4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

10

5 Step 276a. 6-acetyl-3-methyl-2-benzoxazolinone

15 The compound from Example 275 Step a was treated with methyl iodide and NaH in 1:1 THF/DMF for 6 hours at 0 °C to 25 °C. The reaction was quenched with aqueous sodium bicarbonate solution, the mixture was extracted with dichloromethane, and the residue was purified by chromatography to give the title compound.

10 20

Step 276b. 1-(3-hydroxy-4-methylaminophenyl)-ethanone

25 The compound from Step 276a (1.60 g, 8.37 mmol) was dissolved in acetone (70 mL) and treated with 1M aqueous K₂CO₃ solution (25 mL) with heating at reflux overnight. The mixture was neutralized with acid, then extracted with diethyl ether. The solvent was dried (MgSO₄) and removed under vacuum to give the title compound (2.01 g)

30

Step 276c. 7-acetyl-4-methyl-2H-4H-benzo-1,4-oxazin-3-one

20 The compound from Step 276b (2.01 g, 8.37 mmol) was dissolved in DMSO and treated with sodium ethoxide (8.4 mmol) and bromoacetic acid (1.40 g, 8.4 mmol) at room temperature overnight. The mixture was diluted with water and ether, and the title compound was isolated by filtration (0.48 g). MS (M+H), 206.

40

25 Step 276d. 4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

45 Following the procedures of Example 244 Step c, except in step c first substituting the compound from Step 276c for the R¹ reagent of Example 244 Step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the title compound was

50

5

prepared. MS (M+H), 462 (1 Br); IR (cm⁻¹) 3500, 2800-3200, 1690, 1645, 1610, 1590, 1385, 1355.

10

Example 277

5 4-amino-5-(3-bromophenyl)-7-(2,2,4-trimethyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

15

Step 277a. 7-acetyl-2,2,4-trimethyl-2H-4H-benzo-1,4-oxazin-3-one

The compound from Step 276b (2.25 g, 9 mmol) was dissolved in DMSO and
10 treated with sodium ethoxide (9 mmol) and 2-bromo-2-methylpropanoic acid (1.76 g, 9
mmol) at room temperature overnight. The mixture was diluted with water, and the
mixture was extracted with ether/ethyl acetate. The extract was dried ($MgSO_4$), the
solvent was removed under vacuum, and the residue was purified by chromatography
20 (silica gel) to give the title compound (1.33 g) MS (M+H), 234.

25

15

Step 277b. 4-amino-5-(3-bromophenyl)-7-(2,2,4-trimethyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

30 Following the procedures of Example 244 Step c, except in step c first substituting
the compound from Step 277a for the R⁴ reagent of Example 244 Step c, and secondly
20 performing the condensation with ammonium acetate substituting dichloroethane as the
solvent in place of the ethanol solvent in Example 244 step c, the title compound was
35 prepared. MS (M+H), 490 (1 Br); IR (cm⁻¹) 3450, 2900-3100, 1680, 1645, 1610, 1515,
1385, 1365, 1165.

40

25

Example 278

4-amino-5-cyclohexyl-7-(4-(2-dimethylamino)ethyl)-2H-4H-benzo-3-oxo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

45

50

5

Step 278a. 1-(3-hydroxy-4-(dimethylamino)ethyl)phenyl)-ethanone

10

A sample of 6-acetyl-3-(dimethylaminoethyl)-2-benzoxazolinone (from Example 275 Step b) was dissolved in acetone and treated with 1M aqueous K₂CO₃ solution with heating at reflux overnight. The mixture was neutralized with acid, then extracted with diethyl ether. The solvent was dried (MgSO₄) and removed under vacuum to give the title compound.

15

Step 278b. 7-acetyl-4-(dimethylamino)ethyl)-2H-4H-benzo-1,4-oxazin-3-one

20

A sample of the compound from Step 278a (8.94 g, 32 mmol) was dissolved in DMSO and treated with sodium ethoxide (32 mmol) and bromoacetic acid (5.34 g, 32 mmol) at room temperature for 2 days. The mixture was diluted with water then extracted with ether. The extract was dried (MgSO₄), the solvent was removed under vacuum, and the residue was purified by chromatography (silica gel) to give the title compound (1.94 g). MS (M+H), 263.

25

15

Step 278c. 4-amino-5-cyclohexyl-7-(4-(dimethylamino)ethyl)-2H-4H-benzo-3-oxo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

30

Following the procedures of Example 244 Step c, except in step c first substituting 1,1-dicyano-3-cyclohexylethene (prepared according to the method of Moison, et al.

35

(Tetrahedron (1987), 43:537-542) by treating cyclohexane carboxaldehyde with malononitrile in the presence of finely powdered magnesium oxide in dichloromethane) for the R₃ reagent of Example 244 Step c, and substituting the compound from Step 278b for the R⁴ reagent of Example 244 Step c, and also performing the condensation with ammonium acetate but also substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the title compound was prepared. MS (M+H) 447; IR(cm⁻¹) 3400, 2900, 1690, 1610, 1590, 1395.

40

45

50

5

Example 2794-amino-5-(3-bromophenyl)-7-(5-(1-methylethyl)-2-pyridyl)pyrido[2,3-d]pyrimidine

10

Step 279a. 1-(5-methylethyl-2-pyridyl)ethanone

- 5 A solution of 2-acetyl-5-bromopyridine (1.45 g, 7.9 mmol), 2-propenyltrimethyltin (1.77 g, 8.7 mmol), Pd₂(dba)₃ (0.33 g, 0.36 mmol), and tri-2-furylphosphine (0.17 g, 0.72 mmol) in 25 mL of benzene was warmed at 60 °C for 4 hours. The reaction mixture was concentrated and the coupled product was purified by flash chromatography (1.22 g, 96 %). The product was dissolved in 25 mL of EtOH and the solution was purged with a stream of H₂. 10% Palladium on charcoal (50 mg) in 0.5 mL of EtOH was added and the reaction mixture was stirred for 12 h under an atmosphere of H₂. The reaction mixture was filtered and the resulting solution was concentrated under reduced pressure. The title compound, 2, (1.04 g, 84%) was isolated following flash chromatography.

15

20

25

15 Step 279b. 4-amino-5-(3-bromophenyl)-7-(5-(1-methylethyl)-2-pyridyl)pyrido[2,3-d]pyrimidine

- 30 Following the procedures of Example 244 Step c, except in step c substituting the compound from Step 279a for the R¹ reagent of Example 244 Step c, and performing the condensation with ammonium acetate and also substituting dichloroethane as the solvent
- 35 20 in place of the ethanol solvent in Example 244 step c, the title compound was prepared.
MS (M+H) 421 (1Br); IR (cm⁻¹) 3489, 2940, 1545, 1482, 1357.

Examples 280-281

- 40 Following the procedures of Example 244 Step c, except in step c substituting the compound shown below for the R¹ reagent of Example 244 Step c, and performing the condensation with ammonium acetate and also substituting dichloroethane as the solvent
- 45 25 in place of the ethanol solvent in Example 244 step c, the compounds shown in the table below were prepared.

50

5

10

15

20

25

30

35

40

45

50

Ex. No.	Name	R' Reagent (for 7-position)	Analytical Data
280	4-amino-5-(3-bromophenyl)-7-(5-piperidin-1-ylpyrid-2-yl)pyrido[2,3-d]pyrimidine	1-(5-piperidinyl-2-pyridyl)ethanone	MS (M+H), 460 (1Br); IR (cm-1) 3064, 2937, 1556, 1493, 1358
281	4-amino-5-(1-(4-bromophenyl)ethyl)-7-(6-morpholinylpyrid-3-yl)pyrido[2,3-d]pyrimidine	1-(2-morpholinyl-5-pyridyl)ethanone	MS (M+H), 491 (1 Br); IR (cm-1) 1585, 1555, 1505, 1240, 1110, 940

* Prepared as in Ex. 252b, except substituting morpholine for the bis(2-methoxyethyl)amine thereof.

** prepared by treatment of 5-acetyl-2-chloro-pyridine with morpholine in refluxing ethanol.

5

Example 282

4-amino-5-(3-bromophenyl)-7-(4-((N-formylamino)methyl)phenyl)pyrido[2,3-d]pyrimidine

Step 282a. 4-cyanoacetophenone, acetal with 2,2-dimethylpropylene glycol

A sample of 4-cyanoacetophenone (4.35 g, 30 mmol) was dissolved in 150 mL of hexanes, and to this solution were added 2,2-dimethylpropylene glycol (3.44 g, 33 mmol) and a catalytic amount (10 mg) of p-toluene sulfonic acid. The reaction was heated overnight at reflux with a Dean-Stark trap, and an additional portion of glycol (33 mmol) was added. The reaction was continued for 3 hours, then cooled and the solvent was removed. The residue was dissolved in ethyl acetate, and this solution was washed with aqueous NaHCO₃, water and brine, and dried over MgSO₄. The solvent was removed under vacuum to give the title compound (7.46 g).

55

5

10

5

15

25

30

40

50

55

Step 282b. 4-(aminomethyl)acetophenone, acetal with 2,2-dimethylpropylene glycol

The compound from Step 282a (2.31 g, 10 mmol) was dissolved in ether (50 mL) and stirred with lithium aluminum hydride (0.76 g, 20 mmol) at ambient temperature overnight. The reaction was quenched with MgSO₄•10 H₂O, and the mixture was diluted with ether. The mixture was filtered, and the filtrate removed to give the title compound.

Step 282c. 1-(4-(BOC-aminomethyl)phenyl)ethanone

The compound from Step 282b (1.18 g, 5 mmol) was dissolved in THF (20 mL), 1N HCl (20 mL) was added, and the mixture was stirred for 2 days. The volatiles were removed under vacuum, the residue was dissolved in THF (20 mL), and d-tibutyl dicarbonate (2.18 g, 10 mmol) was added. The mixture was stirred at room temperature over a weekend. The solution was diluted with water, and the mixture was extracted with ether and ethyl acetate. The organic extracts were dried (MgSO₄), and the solvent was remove under vacuum to give the title compound.

Step 282d. 4-amino-5-(3-bromophenyl)-7-(4-(N-formylamino)methyl)phenyl)pyrido[2,3-d]pyrimidine

Following the procedures of Example 244, except in step c substituting the compound from Step 282c for the R⁴ reagent of Example 244 Step c, and performing the condensation with ammonium acetate but also substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the title compound was prepared. MS (M+H)⁺ 434 (1 Br); IR (cm⁻¹) 3440, 2700-3150, 1635, 1580, 1380.

25

Example 2834-amino-5-(3-bromophenyl)-7-(4-(1-(N-methylamino)-1-methylethyl)phenyl)pyrido[2,3-d]pyrimidine

5

Step 283a. 4-(1-amino-1-methylethyl)acetophenone

10

CeCl₃ (10 g, 34.9 mmol) was suspended in THF (60 mL), and the mixture was cooled to -78 °C. Methyl lithium (1.4 M, 2 mL) was added, and the mixture was stirred for 20 minutes. Then the compound from Example 282 Step a, (4-cyanoacetophenone acetal with 2,2-dimethylpropylene glycol, 2.31 g, 10 mmol) in 2 mL of THF was added. After stirring for 4 hours, the mixture was allowed to warm to room temperature while stirring for 16 hours. The reaction was quenched with water and ammonium hydroxide, filtered, and the filtrate was extracted with dichloromethane. The solution was dried (MgSO₄), and the solvent was removed to give the title compound.

15

10

20

Step 283b. 4-(1-(N-BOC-amino)-1-methylethyl)acetophenone

25

The compound from Step 283a (2.32 g, 8.77 mmol) was treated sequentially with HCl and di-t-butyl dicarbonate according to the procedure of Example 282 Step c to give the title compound (1.60 g). MS (M+H) 278.

15

30

Step 283c. 4-amino-5-(3-bromophenyl)-7-(4-(1-(N-formylamino)-1-methylethyl)phenyl)pyrido[2,3-d]pyrimidine

35

Following the procedures of Example 244 Step c, except in step c substituting the compound from Step 283b for the R⁴ reagent of Example 244 Step c, and performing the condensation with ammonium acetate but also substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the title compound was prepared. MS (M+H)

462 (1 Br); IR (cm-1) 3440, 1640, 1605, 1580, 1380.

40

25

Example 284

45

4-amino-5-(3-bromophenyl)-7-(4-(1-(N,N-dimethylamino)-1-methylethyl)phenyl)pyrido[2,3-d]pyrimidine

50

5

Step 284a. 4-(1-(dimethylamino)-1-methylethyl)acetophenone

10

The compound from Step 283a (1.18 g, 5 mmol) was dissolved in 5 mL formic acid, and 5 mL of formalin (37%) was added. The mixture was heated at reflux for 4 hours, then cooled and neutralized with 2N Na₂CO₃. The mixture was extracted with dichloromethane. The solution was dried (MgSO₄), and the solvent was removed to give the title compound (0.94 g). MS (M+H) 462 (1 Br); IR (cm⁻¹) 3520, 1640, 1610, 1580, 1375.

15

10

Examples 285-286

20

Following the procedures of Example 157, except substituting the appropriate reagents for the R³ and R⁴ reagents of Example 157 as indicated in the Table below, compounds of Examples 285-286 were prepared. For Example 286, treatment with aqueous HCl was omitted, and the free base was obtained.

25

15

Examples 285-286

30

	Ex. No.	Name	R ³ Reagent (for 5-position)	R ⁴ Reagent (for 7-position)	Analytical Data
35	285	4-amino-5-(3-bromophenyl)-7-(N-acetyl-5-indolinyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-(3-(3-bromophenyl)propene	1-(N-acetyl-5-indolinyl)-ethanone	mp (hydrochloride salt) >270°C. IR (cm ⁻¹) 3445, 3100-2500, 1640, 1605, 1445, 1395, 1325. LRMS [M+H] ⁺ m/z 460, 462.

45

50

5

10

15

286	4-amino-5-cyclohexyl-7-(6-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-3-cyclohexylethen e	1-(6-chloro-3-pyridyl)-ethanone	mp 240-242 °C. IR (cm-1) 3528, 3300, 3086, 2936, 2853, 1645, 1590, 1575, 1565, 1350. LRMS [M+H] ⁺ m/z 340.
-----	--	---------------------------------	---------------------------------	---

Examples 287-300

20

25

30

35

Following the procedures of Example 157, except substituting the appropriate R³ and R⁴ reagents as indicated in the Table below and replacing the formamide or formamidine acetate treatment with treatment with triethyl orthoformate at reflux in the presence of a catalytic amount of ammonium sulfate, followed by cooling to 25 °C and addition of excess ammonia in ethanol, compounds of Examples 287-300 were prepared. After 24 hours, the precipitated amidine compound was filtered and washed with hexanes, then dried under vacuum. The amidine compound was then heated in 1,2-dichloroethane at reflux for 1-8 hours. The reaction mixture was cooled to room temperature and purified by chromatography, and the product was recrystallized if necessary. The treatment with aqueous HCl was omitted in some cases, and the free bases were obtained.

15

Examples 287-300

Ex. No.	Name	R ³ Reagent (for 5-position)	R ⁴ Reagent (for 7-position)	Analytical Data
287	4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-2-methyl-(3-(2-bromophenyl)propene	1-(6-dimethylamino-3-pyridyl)-ethanone	IR (cm-1) 2600-3500, 1650, 1602, 1596, 1520 cm-1. LRMS [M+H] ⁺ m/z 449, 451.

50

5

10

15

20

25

30

35

40

45

50

55

	288	4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-2-methyl-(3-(2-bromophenyl)propene	1-(6-morpholinyl-3-pyridyl)-ethanone	mp (dihydrochloride salt) 213-216 °C. IR (cm-1) 2400-3500, 1660, 1600. LRMS [M+H] ⁺ m/z 491& 493.
	289	4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-(N-methyl-N-formyl)amino-3-phenyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-2-methyl-(3-(2-bromophenyl)propene	1-(6-(N-methyl-N-formyl)amino-3-pyridyl)-ethanone	mp 252-253°C. IR (cm ⁻¹) 3515, 3310, 3200-2800, 1675, 1585, 1560, 1545, 1340. LRMS [M+H] ⁺ m/z 462, 464.
	290	4-amino-5-cyclohexyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-3-cyclohexylethene	1-(6-morpholinyl-3-pyridyl)-ethanone	mp (dihydrochloride salt) 208-210. IR (cm-1) 3490, 3300, 3050-3250, 1620, 1580, 1550, 1490. LRMS [M+H] ⁺ m/z 391.

5

10

15

20

25

30

35

40

50

	291	4-amino-5-((2-bromophenyl)methyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-3-(2-bromophenyl)propane	1-(6-morpholinyl-3-pyridyl)-ethanone	mp (dihydrochloride salt) 201-204 °C. IR (cm-1) 3601, 3500, 3310, 2960, 2850, 1585, 1561, 1502, 1345 LRMS [M+H] ⁺ m/z 477, 479.
	292	4-amino-5-(4-tetrahydropyranyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-3-(4-tetrahydropyranyl)ethene	1-(6-morpholinyl-3-pyridyl)-ethanone	mp (dihydrochloride salt) 213-216 °C. IR (cm-1) 3310, 3060, 2955, 1587, 1559, 1506, 1350. LRMS [M+H] ⁺ m/z 393.
	293	4-amino-5-cyclohexyl-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-3-cyclohexylethene	1-(6-dimethylamino-3-pyridyl)-ethanone	mp (dihydrochloride salt) 272-274 °C. IR (cm-1) 3532, 3294, 3100, 2930, 2853, 1606, 1586, 1560, 1522, 1387. LRMS [M+H] ⁺ m/z 349.

45

55

5

10

15

20

25

30

35

40

45

50

55

	294	4-amino-5-(1-ethylpropyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-3-ethylpentene	1-(6-dimethylamino-3-pyridyl)-ethanone	mp (free base): 223.5-225 °C. IR (cm ⁻¹) 3480, 3000-3470, 2800-3000, 1630, 1610, 1580, 1565, 1520. LRMS [M+H] ⁺ m/z 337.
	295	4-amino-5-cyclopentyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-3-cyclopentylethen	1-(6-morpholinyl-3-pyridyl)-ethanone	IR (cm ⁻¹) 3495, 3320, 3080, 2950, 1645, 1600, 1500, 1400, 1350, 1240. LRMS [M+H] ⁺ m/z 377.
	296	4-amino-5-cyclohexyl-7-(2-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-3-cyclohexylethen	1-(2-chloro-3-pyridyl)-ethanone	IR (cm ⁻¹) 3305, 3155, 2930, 2855, 1590, 1610, 1590, 1545, 1345. LRMS [M+H] ⁺ m/z 340, 342.
	297	4-amino-5-(3,5-dimethylcyclohexyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-3-(3,5-dimethylcyclohexyl)ethene	1-(6-dimethylamino-3-pyridyl)-ethanone	IR (cm ⁻¹) 3310, 3100, 2950, 1605, 1590, 1555, 1390, 1350. LRMS [M+H] ⁺ m/z 377.

5

10

15

20

25

30

35

40

45

50

	298	4-amino-5-((N-(benzyloxycarbonyl)-4-piperidinyl)methyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-(3-(4-benzyloxycarbonyl)piperidin-1-yl)propene	1-(6-morpholinyl-3-pyridyl)-ethanone	IR (cm-1) 3538, 3311, 3032, 2925, 2852, 1696, 1585, 1560. LRMS [M+H] ⁺ m/z 540.
	299	4-amino-5-cyclohexyl-7-(6-bromo-3-pyridyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-3-cyclohexylethen	1-(6-bromo-3-pyridyl)-ethanone	m.p. 250-252 °C, IR (cm-1) 3530, 3298, 3093, 2932, 2856, 1645, 1583, 1569, 1543, 1461, 1346. LRMS [M+H] ⁺ 384, 386.
	300	4-amino-5-cyclohexyl-7-(3-cyanophenyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-3-cyclohexylethen	1-(3-cyanophenyl)-ethanone	m. p. 223-224 °C. IR (cm-1) 3528, 3298, 3075, 2937, 2235, 1645, 1586, 1548, 1567, 1463. LRMS [M+H] ⁺ 332.

* The 1,1-dicyano-3-cyclohexylethene was prepared according to the method of Moison, et al. (Tetrahedron (1987), 43:537-542) by treating cyclohexane carboxaldehyde with malononitrile in the presence of finely powdered magnesium oxide in dichloromethane.

The reagents for the following examples were prepared by this method substituting the compound shown below for the cyclohexane carboxaldehyde used to prepare the reagent of Example 290.

Example 292. tetrahydropyran-4-carboxaldehyde;

Example 294. 2-ethylbutanaldehyde;

55

5

Example 295, cyclopentane carboxaldehyde:

Example 297, 3,5-dimethylcyclohexane carboxaldehyde:

Example 298, N-(phenylmethoxycarbonyl)piperidine-4-carboxaldehyde

10

(this material was prepared from N-(carbobenzyloxy)-4-(2-hydroxyethyl)piperidine

5 (Brehm et al., *Helv.Chim.Acta*, 70; (1987). 1981-1987 by treatment with TEMPO

(2,2,6,6-tetramethylpiperidinyloxy radical) and potassium bromide in

15

dichloromethane at 0 °C to which was added commercial bleach (Clorox) containing sodium bicarbonate).

20

10

Examples 301-305

25

Following the procedures of Example 246, except in step (c) substituting the appropriate reagents for methylamine as indicated in the Table below to prepare the correct R⁴ reagent, and substituting the R³ reagent shown below for the R³ reagent of Example 246 step d, the compounds of Examples 301-305 were prepared. For Example 15 302 only, the condensation solvent was DMSO instead of ethanol and dimethoxyethane.

30

Examples 301-305

Ex. No.	Name	R ¹ reagent	reagent of step c	Analytical Data
35 40 45	301 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-dimethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-(3-(2-bromophenyl)propene	dimethylamine	mp (dihydrochloride salt) >220°C. IR (cm ⁻¹) 3500-2400, 1640, 1610, 1580, 1370. LRMS [M+H] ⁺ m/z 450, 452.

50

5

10

15

20

25

30

35

40

45

50

	302	4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine	1',1'-dicyano-(3-bromostyrene	imidazole sodium salt	mp (tetrahydrochloride salt) >240°C. IR (cm ⁻¹) 3600-2400, 1640, 1610, 1590, 1560, 1415, 1370. LRMS [M+H] ⁺ m/z 445, 447.
	303	4-amino-5-(3-bromophenyl)-7-(6-(azacycloheptanyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine	1',1'-dicyano-(3-bromostyrene	azacycloheptane	mp (dihydrochloride salt) >190°C. IR (cm ⁻¹) 3435, 3100-2400, 1635, 1610, 1590, 1550, 1440, 1370. LRMS [M+H] ⁺ m/z 476, 478.
	304	4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(1-methylethyl))amino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine	1',1'-dicyano-(3-bromostyrene	N-methyl-N-(1-methylethyl)amine	mp (dihydrochloride salt) >210°C. IR (cm ⁻¹) 3435, 3100-2400, 1635, 1610, 1590, 1550, 1410, 1370. LRMS [M+H] ⁺ m/z 450, 452.

55

5

10

15

305	4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine	1,1-dicyano-(3-(2-bromophenyl)propene	morpholine	IR (cm-1) 3475, 3313, 3100, 1650, 1620, 1580, 1555. LRMS [M+H] ⁺ at 492, 494.
-----	---	---------------------------------------	------------	--

Example 306

20 4-amino-5-cyclohexyl-7-(6-(4-acetyl(piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

25 A mixture of 679 mg (2 mmol) of the compound from Example 298 and 1.28 g (10 mmol) of N-acetyl piperazine in 5 mL of DMSO was heated at 110 °C for 5 hours. On cooling a precipitate was deposited, which was collected and washed with 20% methanol and dried to give 647 mg of the product as orange flakes: IR (cm-1) 3522, 3306, 3110, 2925, 2854, 1670, 1650, 1586, 1506. LRMS [M+H]⁺ m/z 432.

10

30

Examples 307-322

35 Following the procedure of Example 306, except substituting the reagent shown in the table below for the N-acetyl piperazine of Example 306, the compounds shown in the table were prepared. The compounds were purified by

15 HPLC chromatography.

40

Ex. No.	Name	reagent	Analytical Data
------------	------	---------	-----------------

45

50

5

10

15

20

25

30

35

40

45

50

55

	307	4-amino-5-cyclohexyl-7-(6-(4-acetyl-1,4-diazacycloheptanyl)-3-pyridyl)pyrido[2,3-d]pyrimidine	1-acetyl-1,4-diazacycloheptane m.p. 169-171 °C. IR (cm-1) 3535, 3309, 3096, 2930, 2854, 1638, 1605, 1587, 1558, 1513. LRMS [M+H] ⁺ 446.
	308	4-amino-5-cyclohexyl-7-(6-(4-methyl-1,4-diazacycloheptanyl)-3-pyridyl)pyrido[2,3-d]pyrimidine	1-methyl-1,4-diazacycloheptane LRMS [M+H] ⁺ 419.
	309	4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(2-(2-pyridyl)ethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine	N-methyl-N-(2-(2-pyridyl)ethyl)amine LRMS [M+H] ⁺ 441.
	3101	4-amino-5-cyclohexyl-7-(6-2-(N-(N',N'-dimethylaminoethyl)-N-methylamino)-3-pyridyl)pyrido[2,3-d]pyrimidine	N,N-dimethyl, N'-methyl-1,2-ethylenediamine LRMS [M+H] ⁺ 421.

5

10

15

20

25

30

35

40

45

50

	311	4-amino-5-cyclohexyl-7-(6-azetidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine	azetidinc	LRMS [M+H] ⁺ 361.
	312	4-amino-5-cyclohexyl-7-(6-(3-(N-methylacetamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine	N-methyl-N-(3-pyrrolidinyl)acetamide	LRMS [M+H] ⁺ 447.
	313	4-amino-5-cyclohexyl-7-(6-(3-(formamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine	pyrrolidine-2-formamide	LRMS [M+H] ⁺ 419.
	314	4-amino-5-cyclohexyl-7-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]deca-n-8-yl)pyrido[2,3-d]pyrimidine	1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one	LRMS [M+H] ⁺ 536.
	315	4-amino-5-cyclohexyl-7-(6-(2-(methoxymethyl)pyrrolidin-1-yl)pyridyl)pyrido[2,3-d]pyrimidine	2-(methoxymethyl)pyrrolidine	LRMS [M+H] ⁺ 420.

55

5

10

15

20

25

30

35

40

45

50

55

	316	4-amino-5-cyclohexyl-7-(6-(N-methoxyethyl-N-propylamino)pyridyl)pyrido[2,3-d]pyrimidine	N-(methoxyethyl)propylamine	LRMS [M+H] ⁺ 421.
	317	4-amino-5-cyclohexyl-7-(N-methyl-N-(2,2-dimethoxyethyl)amino)pyrido[2,3-d]pyrimidine	2-(methylamino)-dimethylacetaldehyde	LRMS [M+H] ⁺ 429.
	318	4-amino-5-cyclohexyl-7-(6-(4-(dimethylamino)piperidinyl)pyridyl)pyrido[2,3-d]pyrimidine	N-(4-piperidyl)-dimethylamine	LRMS [M+H] ⁺ 433.
	319	4-amino-5-cyclohexyl-7-(6-(4-(aminocarbonyl))piperidinyl)pyrido[2,3-d]pyrimidine	piperidine-4-formamide	LRMS [M+H] ⁺ 433.

5

10

15

20

25

30

35

	320	4-amino-5-cyclohexyl-7-(N-methyl-N-(3-(diethylamino)propyl)aminopyrid-3-yl)pyrido[2,3-d]pyrimidine	N ¹ , N ¹ -diethyl-N ² -methyl-1,3-propanediamine	LRMS [M+H] ⁺ 449.
	321	4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(4-pyridyl)ethylamino)pyrid-3-yl)pyrido[2,3-d]pyrimidine	N-methyl-(4-pyridyl)ethylamine	LRMS [M+H] ⁺ 441.
	322	4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(3-pyridylmethyl)amino)pyrid-3-yl)pyrido[2,3-d]pyrimidine	N-methyl-(3-pyridyl)methylamine	LRMS [M+H] ⁺ 427.

Example 3234-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-5-indolyl)pyrido[2,3-d]pyrimidine

The procedures of Example 157 were followed, except substituting 1',1'-dicyano-3-bromostyrene for the R³ reagent and 1-(1-methyl-5-indolyl)-ethanone for the R⁴ reagent. After 24 hours, the precipitated amidine compound was filtered and washed with hexanes, then dried under vacuum. The amidine compound was then heated in 1,2-dichloroethane at reflux for 1-8 hours. The reaction mixture was cooled to room temperature and purified by chromatography, and the product was recrystallized if necessary. The treatment with

50

5

aqueous HCl was omitted, and the free bases were obtained. IR (KBr) cm^{-1} 3500, 1578, 1500; MS m/z 431 ($M+H$)⁺.

10

Example 324

5 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-2,3-dioxo-5-indolyl)pyrido[2,3-d]pyrimidine

15

The title compound was prepared from the compound of Example 323 by oxidation with CrO_3 in sulfuric acid. IR (microscope) 3471, 1765, 1500 cm^{-1} ; MS m/z 461($M+H$)⁺.

10

20

Examples 325-326

25

Following the procedures of Example 157, except substituting the appropriate R^3 and R^4 reagents as indicated in the Table below, compounds of Examples 325-326 were prepared. After 24 hours, the precipitated amidine compound was filtered and washed with hexanes, then dried under vacuum. The amidine compound was then heated in 1,2-dichloroethane at reflux for 1-8 hours. The reaction mixture was cooled to room temperature and purified by chromatography, and the product was recrystallized if necessary. The treatment with aqueous HCl was omitted in some cases, and the free bases were obtained.

30

20

35

Examples 325-326

40

45

Ex. No.	Name	R^3 Reagent (for 5-position)	R^4 Reagent (for 7-position)	Analytical Data
325	4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(1-morpholinyl)phenyl)pyrido[2,3-d]pyrimidine	1',1'-dicyano-3-bromostyrene	1-(3-fluoro-4-(1-morpholinyl)phenyl)-ethanone	IR (microscope) 3443, 3044, 1639, 1606, 1584, 1520, 1362, 1245 cm^{-1} ; MS m/z 480 ($M+H$) ⁺ .

50

5

10

326	4-amino-5-(3-bromophenyl)-7-(4-hydroxy-3-nitrophenyl)pyrido[2,3-d]pyrimidine	1',1'-dicyano-3-bromostyrene	1-(4-hydroxy-3-nitrophenyl)-ethanone	IR (KBr) 3461, 1623, 1579, 1548, 1523, 1353 cm ⁻¹ ; MS m/z 438 (M+H) ⁺ .
-----	--	------------------------------	--------------------------------------	--

15

20

25

10

Following the procedures of Example 244 Step c, except in step c substituting the compound resulting from the reaction of 2-acetyl-5-chloropyridine in refluxing ethanol with the precursor reagent compound (4-piperidinone ethylene ketal) shown below for the R⁴ reagent of Example 244 Step c, and substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the compound shown in the table below was prepared.

30

35

40

Ex. No.	Name	precursor reagent	Analytical Data
327	4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine	4-piperidinone ethylene ketal	IR (microscope) 3091, 1602, 1580, 1558, 1512, 1353, 1236, 1103 cm ⁻¹ ; MS m/z 519 (M+H) ⁺ .

Example 3284-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

45

Treating the compound of Example 327 with dilute HCl, the title compound was prepared. IR (microscope) 3438, 3051, 1645, 1605, 1558, 1450, 1371, 1240 cm⁻¹; MS m/z 475 (M+H)⁺.

50

55

5

10

Following the procedures of Example 327, except in step c substituting the precursor reagent compound shown below for the R⁴ reagent of Example 244 Step c, and substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the compounds shown in the table below were prepared.

15

Examples 329-331

20

25

30

35

40

45

10

Ex. No.	Name	precursor reagent	Analytical Data
329	4-amino-5-(3-bromophenyl)-7-(6-(4-formylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine	piperazine	IR (KBr) 3489, 1674, 1602, 1581, 1559, 1503, 1233, 1004 cm ⁻¹ ; MS m/z 491 (M+H) ⁺ .
330	4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine	1-methylpiperazine	IR (microscope) 3438, 3051, 1540 cm ⁻¹ ; MS m/z 477 (M+H) ⁺ .
331	4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidin	thiomorpholine	IR (KBr) 3486, 1602, 1581, 1560, 1502, 1228 cm ⁻¹ ; MS m/z 479 (M+H) ⁺ .

50

5

Example 3324-amino-5-(3-bromophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

10

The compound of Example 331 was treated with 4-chloroperbenzoic acid in methanol and dichloromethane to give the title compound. IR (microscope) 3471, 1601, 1581, 1562, 1510, 1353, 1316, 1285, 1122 cm⁻¹; MS m/z 511(M+H)⁺.

15

Example 3334-amino-5-(2-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

20

Step 333a. 1',1'-dicyno-2-bromostyrene

The title compound was prepared by condensation of 2-bromobenzaldehyde with malononitrile and MgO in dichloromethane by the standard procedure of Broekhuis et al. (Recl. J. R. Neth. Chem. Soc., 99: 6-12 (1980)).

25

15

Step 333b. 5-acetyl-2-morpholinylpyridine

30

The title compound was prepared by the reaction of 5-acetyl-2-chloropyridine with morpholine in refluxing ethanol.

35

Step 333c. 4-(2-bromophenyl)-3-cyano-6-morpholinylpyridine-2-amine

40

The title compound was prepared by condensation of 1',1'-dicyno-2-bromostyrene with 5-acetyl-2-morpholinylpyridine and ammonium acetate in dichloroethane at reflux. After the reaction was complete (TLC), the mixture was cooled, and the solvent was removed. The residue was triturated with methanol to give the product.

45

Step 333d. 4-amino-5-(2-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

50

A sample of 4-(2-bromophenyl)-3-cyano-6-morpholinylpyridine-2-amine was heated at 180-190 °C in formamide. The reaction was monitored by TLC, and when the reaction was complete the mixture was cooled to room temperature. The product was

55

5

10

20

allowed to precipitate, then recovered by filtration and washed with water. Additional product was extracted from the filtrate. The product was purified by column chromatography eluting with 10% MeOH/CH₂Cl₂. IR (microscope) 3493, 1547, 1109cm⁻¹; MS m/z 464 (M+H)⁺.

5

15 Following the procedures of Example 333, except in Step a substituting the precursor aldehyde reagent shown below for the 2-bromobenzaldehyde of Example 333 Step a, and carrying the product forward as in procedures 333 Steps b-d, the compounds

10 shown in the table below were prepared.

Examples 334-336

Ex. No.	Name	precursor aldehyde reagent	Analytical Data
334	4-amino-5-(3-bromo-4-methoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine	3-bromo-4-methoxybenzaldehyde	IR (microscope) 3486, 1600, 1575, 1562, 1500, 1260, 1237 cm ⁻¹ ; MS m/z 493 (M+H) ⁺ .
335	4-amino-5-(4-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine	4-bromobenzaldehyde	IR (microscope) 3497, 1532, 1098cm ⁻¹ ; MS m/z 464 (M+H) ⁺ .

50

5

10

336	4-amino-5-(3-chlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine	3-chlorobenzaldehyde	IR (microscope) 3484, 1500, 1034cm ⁻¹ ; MS (FAB) m/z 587 (M+H) ⁺ .
-----	---	----------------------	--

15

Example 3374-amino-5-(3-bromophenyl)-7-(5-chloro-6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

20

- Following the procedures of Example 333, except in Step a substituting 3-bromobenzaldehyde for the 2-bromobenzaldehyde, in Step b substituting 5-acetyl-2,3-dichloropyridine for the 5-acetyl-2-chloropyridine to give 5-acetyl-3-chloro-2-morpholinylpyridine, and substituting 5-acetyl-3-chloro-2-morpholinylpyridine for the 5-acetyl-2-morpholinylpyridine in step c, then carrying the product forward as in Example 333 Step d, the title compound was prepared. IR (microscope) 3493, 1635, 1585, 1555, 1492, 1340, 1241, 1113 cm⁻¹; MS m/z 497 (M+H)⁺.

30

Example 3384-amino-5-(3-bromophenyl)-7-(6-(N-oxidomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

35

- The title compound was prepared by treating the compound of Example 134 with hydrogen peroxide in acetic acid according to standard procedures. IR (microscope) 3486, 1579, 1552, 1353, 1121, 1020 cm⁻¹; MS m/z 479 (M+H)⁺.

40

45

50

55

5

Example 339

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine

10

5 Step 339a. 1',1'-dicyano-3-bromostyrene

15 The title compound was prepared by condensation of 3-bromobenzaldehyde with malononitrile and MgO in dichloromethane by the standard procedure of Broekhuis et al. (Recl. J. R. Neth. Chem. Soc., 99: 6-12 (1980)).

20

10 Step 339b. 5-acetyl-2-(N-(2-ethoxyethyl)amino)pyridine

25 The title compound was prepared by the reaction of 5-acetyl-2-chloropyridine with 2-ethoxyethylamine in refluxing ethanol.

25

15 Step 339c. 4-(3-bromophenyl)-3-cyano-6-(N-(2-ethoxyethyl)amino)pyridine-2-amine

30

15 The title compound was prepared by condensation of 1',1'-dicyano-2-bromostyrene with 5-acetyl-2-morpholinylpyridine and ammonium acetate in dichloroethane at reflux. After the reaction was complete (TLC), the mixture was cooled, and the solvent was removed. The residue was triturated with methanol to give the product.

35

20 Step 339d. 4-amino-5-(2-bromophenyl)-7-(6-(N-(2-ethoxyethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine

40

35 A sample of the compound from Step 239d was treated according to the procedure of Example 233d to give the title compound. IR (microscope) 3301, 1610, 1579, 1543, 1346, 1304, 1120 cm⁻¹; MS m/z 481 (M+H)⁺.

25

45

50

5

Example 340

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-N-formylamino)-3-pyridyl)pyrido[2,3-d]pyrimidine

10

This compound was isolated by chromatography as a product of the reaction described in Example 239 Step d. IR (microscope) 3306, 1679, 1596, 1577, 1548, 1493, 1352, 1125 cm⁻¹; MS m/z 509 (M+H)⁺.

15

Example 341

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-3-pyridyl-N-oxide)pyrido[2,3-d]pyrimidine

20

The title compound was prepared by treating the compound of Example 341 with hydrogen peroxide in acetic acid according to standard procedures. IR (microscope) 3296, 1628, 1560, 1411, 1353 cm⁻¹; MS m/z 497 (M+H)⁺.

25

15

Example 342

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

30

The title compound was prepared from the compound of Example 328 by reduction with Lithium Aluminum Hydride, and subsequent workup according to standard procedures. IR (microscope) 3349, 1510, 1116 cm⁻¹; MS m/z 478 (M+H)⁺.

35

Example 343

1-(5-(4-amino-5-(3-bromophenyl)pyrido[2,3-d]pyrimidin-7-yl)-2-pyridyl)-piperidine-4-phosphate, disodium salt

40

The title compound was prepared from the compound of Example 342 by treatment with POCl₃, and subsequent workup according to standard procedures. IR (microscope) 3498, 1500, 1444 cm⁻¹; MS m/z 556 (M+H)⁺.

45

50

5

Example 3444-amino-5-(3-bromophenyl)-7-(6-(2-hydroxy)morpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

10

The title compound was prepared from the compound of Example 339 by oxidation of the free hydroxy group to an aldehyde with TEMPO reagent. During workup of the mixture, the compound self-condensed to give the title compound.

15

MS m/z 492 (M+CH₃OH-H₂O)'.

Example 3454-amino-5-(3-bromophenyl)-7-(4-methylen(piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

20

The title compound was prepared from the compound of Example 328 by treatment with methyl triphenylphosphine bromide at -78 °C in DMSO. After quenching and warming the mixture to room temperature, the title compound was extracted, then purified by chromatography. IR (microscope) 3055, 1602, 1559, 1508, 1440, 1344, 1174 cm⁻¹; MS m/z 473 (M+H)'.

30

Example 3464-amino-5-(3-bromophenyl)-7-(4-hydroxy-4-(hydroxymethyl)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

35

The title compound was prepared from the compound of Example 345 by treatment with OsO₄ in DMSO at room temperature. After quenching, the title compound was extracted, then purified by chromatography. IR (microscope) 3304, 1603, 1580, 1557, 1509, 1352, 1241 cm⁻¹; MS m/z 507 (M+H)'.

40

25

Example 3474-amino-5-(cyclohexyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

45

Step 347a. 1,1-dicyano-3-cyclohexylethene

50

5

10

The 1,1-dicyano-3-cyclohexylmethene was prepared according to the method of Moison, et al. (*Tetrahedron* (1987), 43:537-542) by treating cyclohexane carboxaldehyde with malononitrile in the presence of finely powdered magnesium oxide in dichloromethane.

15

Step 347b. 2-acetyl-5-(4,4-ethylenedioxypiperidinyl)pyridine

A sample of 2-acetyl-5-chloropyridine was treated in refluxing ethanol with 4-piperidinone ethylene ketal to give the title compound.

20

Step 347c. 4-amino-5-cyclohexyl-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Following the procedures of example 339 Step c, except substituting the compounds from Step 347a and 347b for the compounds of Steps 339a and 339b, and carrying the product forward according to the procedure of example 339 Step d, the title

25 15 compound was prepared. IR (microscope) 2929, 1604, 1585, 1557, 1514, 1426, 1344, 1238, 1106 cm⁻¹; MS m/z 447 (M+H)⁺.

30

Example 348

4-amino-5-cyclohexyl-7-(6-(4-oxo-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

20 The title compound was prepared from the compound of Example 347 by treatment with dilute HCl in ethanol. The title compound was purified by chromatography. IR (microscope) 2928, 1715, 1603, 1585, 1559, 1507, 1344, 1226 cm⁻¹; MS m/z 403 (M+H)⁺.

40

25

Example 349

4-amino-5-cyclohexyl-7-(6-(4-methylenepiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

45 The title compound was prepared from the compound of Example 348 by treatment with methyl triphenylphosphine bromide at -78 °C in DMSO. After quenching and warming the mixture to room temperature, the title compound was extracted, then

50

5

purified by chromatography. IR (microscope) 2929, 1604, 1584, 1557, 1506, 1342, 1239 cm⁻¹; MS m/z 401 (M+H)⁺.

10

Example 3505 4-N-(iminomethyl)amino-5-cyclohexyl-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine

15

This compound was isolated from the reaction mixture of Example 293 as a side product: IR (cm⁻¹) 3289, 3089, 2930, 2841, 1674, 1606, 1559, 1531. LRMS [M+H]⁺ m/z 376.

10
20Example 35125 (S)-4-amino-S-(3-bromophenyl)-7-(6-(O-methyl-2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine

25

Prepared as described for Examples 2-156; using (S)-1-(6-(O-methyl-2-pyrrolidinemethanol)-3-pyridinyl)ethanone as R₄ reagent (for position 7) and 3-bromobenzaldehyde for R₃ reagent (for 5-position).

30

MS (ESI(+)) 489/491 (M+H⁺; ⁷⁹Br/⁸¹Br);
IR (KBr pellet) ν_{max} 3484, 3203, 1603, 1581, 1556 cm⁻¹.

20

Example 35235 (S)-4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxy ethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine

40

Prepared as described for Examples 2-156; using (S)-1-(6-(2-pyrrolidinemethanol)-3-pyridinyl)ethanone as R₄ reagent (for position 7) and 3-bromobenzaldehyde for R₃ reagent (for 5-position).

45

MS (ESI(+)) 477/479 (M+H⁺; ⁷⁹Br/⁸¹Br);
IR (KBr pellet) ν_{max} 3487, 3303, 3208, 2949, 1605, 1577, 1558, 1510, 1415, 1351, 1244, 1158, 828, 704 cm⁻¹.

30

Example 353

50

5

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine

10

Prepared as described for Examples 2-156, using 1-(6-(4-hydroxypiperidine)-3-pyridinyl)ethanone as R₄ reagent (for position 7) and 2-bromobenzaldehyde for R₃ reagent (for 5-position).

15

MS (ESI(+)) 477/479 (M+H⁺; ⁷⁹Br/⁸¹Br);

20

IR (KBr pellet) ν_{max} 3485, 3298, 3198, 2938, 2848, 1600, 1574, 1557, 1351, 1225, 1024, 766 cm⁻¹.

25

Example 354

30

4-amino-5-(4-fluorophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine

35

Prepared as described for Example 327: using 4-fluorobenzaldehyde instead of 3-bromobenzaldehyde as precursor reagent as described in example 244 Step C.

15 MS (ESI(+)) 459 (M+H⁺);

IR (KBr pellet) ν_{max} 3487, 3299, 3066, 1959, 1604, 1577, 1559, 1510, 1355, 1235, 1107, 943, 897, 792 cm⁻¹.

40

Example 355

45

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine

Prepared as described for Examples 301-305, using 4-hydroxypiperidine as reagent for Step C (to prepare correct R₄ reagent).

MS (ESI(+)) 478/480 (M+H⁺; ⁷⁹Br/⁸¹Br);

50

IR (KBr pellet) ν_{max} 3487, 3312, 1576, 1549, 1486, 1353, 1081 cm⁻¹.

Example 356

55

4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine

30 Prepared as described for Examples 301-305; using 4-piperidinone ethylene ketal

50

5

as reagent for Step C (to prepare correct R₁ reagent).

MS (ESI(+)) 520/522 (M+H⁺; ⁷⁹Br⁸¹Br);

IR (KBr pellet) ν_{max} 3476, 3297, 1574, 1561, 1461, 1354, 1145, 1103 cm⁻¹.

10

5

Example 357

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazolyl)pyrido[2,3-d]pyrimidine

15

A solution of the product from 357d (2.49 g, 5.30 mmol) in o-dichlorobenzene (15 mL) was heated to reflux overnight. The reaction mixture was cooled to room temperature, the solid collected by filtration and purified by silica gel chromatography (elution with 3% methanol:dichloromethane) to provide 1.06 g (43%) of the desired title product as a yellow solid. mp: >280 °C; MS (DCI/NH₃) m/z 469/471 (M+H)⁺; IR (microscope) 3481, 2046, 1506, 1491, 1116 cm⁻¹.

20

25

357a: 2-morpholinylthiazole

30

2-bromothiazole (12.63 g, 77.00 mmol) in morpholine (30.0 mL) was sealed into a tube and heated to 100 °C for 3 days. The mixture was cooled, partitioned between water and dichloromethane, the layers separated and the organic phase dried (Na₂SO₄) and concentrated to afford 12.5 g (95%) of the desired compound as a brown oil. Material used directly in the next reaction. MS (DCI/NH₃) m/z 171 (M+H)⁺.

20

35

357b: 5-acetyl-2-morpholinylthiazole

40

A solution of the product from Example 357a (7.20 g, 42.3 mmol) in tetrahydrofuran (80 mL) at -78 °C was treated with N-BuLi (2 M in hexanes, 23.5 mL). After 30 minutes, the reaction mixture was transferred via cannula to a solution of acetic anhydride (10 mL) in tetrahydrofuran (50 mL) at -60 °C and stirred for 1 hour. The slurry was then warmed to room temperature for an additional 30 minutes, quenched with saturated sodium bicarbonate and extracted with diethyl ether. The organic phase was dried (Na₂SO₄), concentrated and purified by silica gel chromatography (elution with 50% dichloromethane/ethyl acetate) to provide 3.70 g (41%) of the desired compound. MS (DCI/NH₃) m/z 213 (M+H)⁺.

50

5

10 357c: 4-(3-Bromophenyl)-3-cyano-6-(2-morpholinethiazolo)pyridine-2-amine
A slurry of the product from 357b (4.91 g, 23.1 mmol) and ammonium acetate
(9.75 g, 127 mmol) in 1,2-dichloroethane (50 mL) was treated with 2-(3-
5 bromobenzylidene)malononitrile (10.78 g, 46.3 mmol; J. Am. Chem. Soc. 1949, 71, 2949)
and the mixture heated to reflux overnight. The solution was cooled to room temperature.
15 hexanes (50 mL) added and stirring continued for 3 hours. The solid was collected by
filtration, washed with methanol and dried to provide 4.57 g (45%) of the desired material
as an orange solid. MS (DCI/NH₃) m/z 442/444 (M+H)⁺.

10 20 357d: 4-(3-Bromophenyl)-3-cyano-6-(2-morpholinethiazolo)pyridine-2-amidine
A solution of the product from 357c (1.50 g, 3.39 mmol) and triethylorthoformate
(34 mL) with a catalytic amount of ammonium sulfate was heated to reflux for 6 hours.
25 The dark mixture was cooled, ammonia in ethanol (2 M, 70 mL) added and the mixture
15 stirred overnight. The solid product was collected by filtration and dried to provide 1.17 g
(73%) of the desired product as a yellow solid. MS (DCI/NH₃) m/z 469/471 (M+H)⁺.

30

Example 358

20 4-amino-5-(N-methyl-3-indolyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine
Prepared as described for Examples 2-156; using 1-(6-morpholinyl-3-
35 pyridinyl)ethanone as R₁ reagent (for position 7) and N-methylindole-3-carboxaldehyde
for R₂ reagent (for 5-position).
MS (DCI/NH₃) 438 (M+H)⁺;
IR (mic) 3453, 1641, 1556, 1244, 1120 cm⁻¹.

40

25

Example 359

45 4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine
A suspension of Example 328 (282 mg, 0.593 mmol) in absolute ethanol (3 mL)
50 30 was treated sequentially with ethoxyamine hydrochloride (64 mg, 0.65 mmol), and 2 drops

55

5

conc. aq. HCl, heated to reflux 1.5 hours, cooled and partitioned, between CH₂Cl₂ (25 mL) and saturated NaHCO₃ (15 mL). The separated aqueous phase was extracted with CH₂Cl₂ (1 x 10 mL), and the combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The crude product was purified by flash chromatography eluting with 5% MeOH/CH₂Cl₂ to yield 240 mg (78%) of the designated compound.

¹H NMR (300 MHz, DMSO-d₆) δ 1.19 (t, 3H), 2.41 (m, 2H), 2.58 (m, 2H), 3.77-3.86 (m, 4H), 4.02 (q, 2H), 6.99 (d, 1H), 7.50-7.60 (m, 2H), 7.79 (dt, 1H), 7.85 (m, 2H), 8.47 (dd, 1H), 8.53 (s, 1H), 9.08 (d, 1H);

MS (DCI/NH₃) m/e 518/520 (M+H)⁺;

Anal. calcd for C₂₁H₂₄BrN₂O: C, 57.92; H, 4.67; N, 18.91. Found: C, 57.69; H, 4.66; N, 18.65.

Example 360

25 4-amino-5-(3-bromophenyl)-7-(6-(4-ethylcarbomethoxyminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine

15 Prepared as described for Example 359, substituting carbomethoxylamine for ethoxyamine.

30 ¹H NMR (300 MHz, DMSO-d₆) δ 1.20 (t, 3H), 2.42 (m, 2H), 2.65 (m, 2H), 3.77-3.90 (m, 4H), 4.13 (q, 2H), 4.61 (s, 2H), 7.01 (d, 1H), 7.55 (m, 2H), 7.79 (dt, 1H), 7.86 (m, 2H), 20 8.48 (dd, 1H), 8.53 (s, 1H), 9.09 (d, 1H); MS (DCI/NH₃) m/e 576/578 (M+H)⁺;

35 Anal. calcd for C₂₁H₂₆BrN₂O·0.5 H₂O: C, 55.39; H, 4.65; N, 16.75. Found: C, 55.66; H, 4.61; N, 16.37.

Example 361

40 4-(N-(2,3-dihydroxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine

45 Example 134 formamide complex (200 mg, 0.339 mmol) and 3-amino-1,2-propanediol (155 mL, 2.0 mmol) were placed in a 50 mL round-bottomed flask furnished with a magnetic stirbar. DMSO (dimethyl sulfoxide) (6 mL) was added. The mixture was 50 then heated to 120 °C for about 10 min until a homogeneous solution was formed.

5

10

15

20

30

35

40

50

Catalytic amount of acetic acid was then added, and the reaction mixture was allowed to stir at 120 °C for about 1.5 days. DMSO was removed under vacuum. The residue was dissolved in CH₂Cl₂, and washed with water, NaHCO₃ (saturated), water, and then dried over Na₂SO₄. The crude mixture was first purified by column chromatography (SiO₂), 10% MeOH/CH₂Cl₂). The desired product was collected and was subjected to another column chromatographic purification (SiO₂, ethyl acetate and then 25% NCCH₃, 7.5% MeOH and 67.5% CH₂Cl₂) to give a pure yellow solid (60 mg, 29% yield; M.P. 189-191 °C). MS (ESI(+)) = 537/539 (M+H)⁺; ⁷⁹Br/⁸¹Br; IR (MIC) ν_{max} = 3433, 3354, 2914, 2853, 1568, 1506, 1236, 1114, 945 cm⁻¹.

10

Example 3624-(N-(3-morpholinylpropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 360, but replacing 3-amino-1,2-propanediol

with 4-(3-aminopropyl)morpholine.

MS (ESI(+)) = 590/592 (M+H)⁺; ⁷⁹Br/⁸¹Br;

IR (MIC): ν_{max} = 3433, 2959, 2854, 1567, 1506, 1235, 1117, 945 cm⁻¹.

Example 3634-(N-(2-(4-imidazolyl)ethyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 360, but replacing 3-amino-1,2-propanediol with histamine.

MS (ESI(+)) = 557/559 (M+H)⁺; ⁷⁹Br/⁸¹Br;

IR (MIC) ν_{max} = 3433, 3091, 2954, 2893, 2854, 1571, 1564, 1505, 1235, 1123, 944 cm⁻¹.

Example 3644-(N-(3-carboxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine

55

5

Prepared as described for Example 360, but replacing 3-amino-1,2-propanediol with 3-aminopropionic acid (β -alanine).

10

MS (ESI(+)) = 535/537 (M+H $^+$; $^{79}\text{Br}/^{81}\text{Br}$);

15

IR (MIC) ν_{max} = 3429, 3051, 2959, 2855, 2528, 1927, 1718, 1585, 1559, 1352, 1332, 1236, 1118, 944 cm^{-1} .

15

Example 365

4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

20

Prepared as described for Example 328; substituting Example 356 for Example 327.

25

MS (APCI+) m/z 475 (M+H) $^+$;

^1H NMR (300 MHz, DMSO-d₆) δ 8.60(s, 1H), 8.45(d, 1H), 8.28(s, 1H), 7.85 (m, 2H), 7.50 (m, 3H), 4.10 (m, 4H).

30

15

Example 366

4-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

35

Prepared as described for Example 359; substituting Example 365 for Example 328 and 4-aminomorpholine for ethoxylamine hydrochloride.

40

MS (APCI+) m/z 560 (M+H) $^+$;

45

^1H NMR (300 MHz, DMSO-d₆) δ 8.59(s, 1H), 8.40(d, 1H), 8.26(s, 1H), 7.84 (m, 2H), 7.55 (m, 3H), 3.93 (m, 4H), 3.68 (m, 4H), 2.75 (m, 2H), 2.63 (m, 4H), 2.47 (m, 2H)

50

Example 367

4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

step a 4-amino-5-(3-bromo phenyl)-7-(6-chloro-3-pyridazinyl) pyrido[2,3-d]pyrimidine

55

Prepared by a modification of the method of Example 333 step C, a mixture of 22 mmol of 3-acetyl-6-chloropyridazine (Example 246), 26 mmol of 1-(3-bromophenyl) 1,1-dicyanoethylene, and 110 mmol of ammonium acetate in 150 mL of dichloroethane was

5

heated at reflux for an hour to give the intermediate amino cyanopyridine, which was purified by flash column chromatography. By a modification of the method of Example 287, the intermediate 2-amino-3-cyano-4-(3-bromo phenyl)-6-((6-chloro) pyridazin-3-yl)pyridine was heated in 40 mL of triethylorthoformate with 1 mmol of ammonium sulfate for one hour. A 2M solution of ammonia in ethanol was added (30 mL) stirring, and after 14 hours, the solid amidine intermediate was collected by filtration and dried in vacuo. The amidine intermediate was then heated in 25 mL of 1,2-dichlorobenzene at 120 °C for two hours. On cooling, a precipitate was deposited. Ether was added, and the precipitate was collected by filtration, washed with ether and dried.

10

15 10 M/z [M+H]⁺ C₁₁H₁₀N₆BrCl at 413.414,415.

15

20 ¹H NMR (CD₃CO₂D) δ 8.72 (d, J = 8.7 Hz, 1 H), 8.64 (s, 1 H), 8.48 (s, 1 H), 7.73 (d, J = 8.7 Hz, 1 H), 7.70 (t, J = 1.0 Hz, 1 H), 7.64 (dt, J = 8.1, 1.0 Hz), 7.45 (dt, J = 8.1, 1.0 Hz, 1 H), 7.42 (m, 1H).

20

25 15 4-amino-5-(3-bromophenyl)-7-(6-(1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

30

30 A solution of 0.73 mmol of 4-amino-5-(3'-bromo phenyl)-7-(6-(chloro) pyridaziN-3-yl) [2,3-d] pyridopyrimidine (prepared in step a), 3.1 mmol of (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane (Aldrich Chemical Co.), and 2.4 mmol of potassium carbonate was 20 heated at 120 °C in DMSO for 14 hours, then cooled and poured into 10 mL of water. The mixture was partitioned between dichloromethane and water, and the organic phase 35 was dried (Na₂SO₄), and concentrated in vacuo to give the title compound. This material was recrystallized from chloroform/methanol and converted to the hydrochloride salt by lyophilization from 12 mL of 2.5 M HCl.

40

25 mp 222-226 °C;

CHN calculated for C₂₂H₁₈N₆OBr(3.0 HCl): C 45.11, H 3.61, N 16.74; found: C 45.00, H 3.90, N 16.82. MS [M+H]⁺ at 478;

45

IR 3434, 3056, 1640, 1610, 1558, 1376 cm⁻¹.

30

Example 368

50

5

4-amino-5-(3-bromophenyl)-7-(6-(4-methoxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

10

Prepared as described for Example 359 substituting Example 365 for Example 328 and methoxylamine hydrochloride for ethoxylamine hydrochloride.

15

MS (ESI+) m/z 504 (M+H)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 8.59 (s, 1H), 8.40 (d, 1H), 8.26 (s, 1H), 7.82 (m, 2H), 7.54 (m, 3H), 3.90 (m, 4H), 3.77 (s, 1H), 2.62 (m, 2H), 2.47 (m, 2H)

Example 369

20

4-amino-5-(3-bromophenyl)-7-(6-phenylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine

25

Sodium and benzyl alcohol were heated at 60 °C in toluene for 3 hours. It was cooled to room temperature and added to a suspension of 4-amino-5-(3-bromo phenyl)-7-(6-chloro-3-pyridazinyl) pyrido[2,3-d]pyrimidine (prepared in Example 367) in anhydrous DMSO to give the title compound. Treatment with 1M HCl ether in chloroform and methanol at room temperature provided the HCl salt.

30

MS (ESI+) m/z 485 (M+H)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 10.07 (bs, 1H), 8.95 (s, 1H), 8.59 (d, 1H), 8.50 (s, 1H), 7.95-7.30 (m, 10H), 5.63 (s, 2H)

Example 370

35

4-amino-5-(3-bromophenyl)-7-(6-(4-methoxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Step a 2-amino-3-cyano-4-(3-bromophenyl)-6-(6-chloro-3-pyridyl)pyridine

Prepared as described in Example 244 substituting 5-acetyl-2-chloropyridine for 5-acetyl-1-methylindoline in step c.

40

25

Step b 4-amino-5-(3-bromophenyl)-7-(6-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine

50

2-Amino-3-cyano-4-(3-bromophenyl)-6-(6-chloro-3-pyridyl)pyridine prepared in step a was reacted with 10 eq. of N,N',N"-methylidynetrisformamide in formamide at 125° for 3 days. The slurry was cooled, poured into 3 volumes of water, and the resulting solid

5

was collected by filtration and washed with water. The chloropyridyl product was dried under vacuum and used without further purification.

10

step c 4-methoxypiperidine

15

5 4-Hydroxypiperidine is treated with 1 eq. of Boc_2O in CH_2Cl_2 and stirred at room temperature for 5 min. The solution is then washed with water and brine, dried over Na_2SO_4 , and concentrated in vacuo. The protected species is then dissolved in DMF and treated with 7 eq. of NaH. The mixture is stirred for 5 min. then methyl iodide (2 eq) is added, and the reaction is stirred at room temperature overnight. After this time, it is

20

10 quenched with water and extracted with 2:1 ether-hexanes. The organic solution is dried (Na_2SO_4) and concentrated in vacuo. The oil thus obtained is finally stirred in 4M HCl-dioxane for 30 minutes. The solvent was removed in vacuo, then the residue was basified with 50% aq. NaOH solution and extracted with ether. Drying (Na_2SO_4) of the extracts, followed by removal of the solvent in vacuo, afforded 4-methoxypiperidine.

25

15

Step d.

30

3.0 equivalents of 4-methoxypiperidine (step c) and 1 equivalent of 4-amino-5-(3-bromophenyl)-7-(6-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine (step b) were stirred in DMSO at 100° for 16 hours. The mixture was cooled, quenched with 3 volumes of water, and the precipitated solid was collected by filtration and washed with water. Purification by recrystallization afforded the title compound. ^1H NMR (300 MHz, d_6 -DMSO) δ 9.05 (d, 1H), 8.52 (s, 1H), 8.42 (dd, 1H), 7.84 (d, 1H), 7.83 (s, 1H), 7.78 (dt, 1H), 7.54 (2 overlapping m, 2H), 6.99 (br d, 1H), 4.07 (m, 2H), 3.45 (m, 2H), 3.36 (m, 1H), 3.29 (s, 3H), 1.92 (m, 2H), 1.46 (m, 2H); MS (ESI) m/z 491/493 ($M^+ + \text{H}$, $^{79}\text{Br}/^{81}\text{Br}$).

40

25

Example 371

4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranloxy)iminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

50

5

Prepared as described for Example 359; substituting Example 365 for Example 328 and O-tetrahydro-2H-pyran-4-yl-hydroxylamine hydrochloride (JP 94-177353 19940729) for ethoxylamine hydrochloride.

10

MS (ESI+) m/z 574 (M+H)⁺;

15 ¹H NMR (300 MHz, CDCl₃-d1) δ 8.78 (s, 1H), 8.69 (d, 1H), 8.59 (s, 1H), 7.71 (m, 2H), 7.46 (m, 2H), 7.10 (d, 1H), 4.26 (m, 1H), 3.98 (m, 6H), 3.53 (m, 2H), 2.79 (m, 2H), 2.59 (m, 2H), 2.00 (m, 2H), 1.69 (m, 2H)

Example 372

20 10 4-amino-5-(3-bromophenyl)-7-(6-isobutoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Sodium isobutoxide was made by heating sodium and isobutanol at 60°C for 45 minutes. 4-amino-5-(3-bromo phenyl)-7-(6-chloro-3-pyridazinyl) pyrido[2,3-d]pyrimidine (prepared as in Example 367) was added to this mixture and heated at 60°C for 2 hours to give the title compound.

25 15 MS (APCI+) m/z 451 (M+H)⁺;

30 30 ¹H NMR (300 MHz, DMSO-d₆) δ 10.07 (bs, 1H), 8.96 (s, 1H), 8.53 (s, 1H), 8.52 (d, 1H), 7.95 (m, 1H), 7.85 (m, 1H), 7.60 (m, 3H), 4.34 (d, 2H), 2.15 (m, 1H), 1.05 (d, 6H)

Example 373

35 20 4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 359; substituting Example 365 for Example 328 and 4-amino-4-N-methylpiperazine for ethoxylamine hydrochloride.

40 25 MS (APCI+) m/z 575 (M+H)⁺;

30 40 ¹H NMR (300 MHz, DMSO-d₆) δ 8.59 (s, 1H), 8.42 (d, 1H), 8.27 (s, 1H), 7.84 (m, 2H), 7.55 (m, 3H), 3.92 (m, 4H), 2.71 (m, 4H), 2.63 (m, 4H), 2.43 (m, 4H), 2.19 (s, 3H)

Example 374

45 30 4-amino-5-(3-bromophenyl)-7-(6-(4-tetrahydropyranloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

50

5

Prepared as described for Example 369; substituting tetrahydro-4H-pyran-4-ol for benzyl alcohol.

10

MS (FAB+) m/z 479 (M+H)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 9.80 (bs, 1H), 8.85 (s, 1H), 8.56 (d, 1H), 8.52 (s, 1H), 7.93 (m, 1H), 7.84 (m, 1H), 7.70-7.50 (m, 3H), 5.51 (m, 1H), 3.91 (m, 2H), 3.55 (m, 2H), 2.13 (m, 2H), 1.77 (m, 2H)

15

Example 375

4-amino-5-(3-bromophenyl)-7-(6-morpholinylethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine

20

Prepared as described for Example 369; substituting N-(2'-hydroxylethyl)-morpholine for benzyl alcohol.

25

MS (FAB+) m/z 508 (M+H)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 12.10 (bs, 1H), 10.05 (bs, 1H), 8.92 (s, 1H), 8.57 (d, 1H), 8.48 (s, 1H), 7.95-7.52 (m, 5H), 7.45 (bs, 2H), 5.05 (m, 2H), 3.97 (m, 4H), 3.69 (m, 2H), 3.60-3.18 (m, 4H)

30

Example 376

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

35

Treatment of N-Boc-4-hydroxypiperidine with sodium hydride and ethyl iodide gave N-Boc-4-ethoxypiperidine, which was treated with 4M HCl in dioxane to give 4-ethoxypiperidine.

40

The title compound was prepared as described for Example 367 substituting 4-ethoxypiperidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, followed by treatment with 1M HCl ether.

45

MS (FAB+) m/z 506 (M+H)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 10.10 (bs, 1H), 8.90 (s, 1H), 8.38 (s, 1H), 8.26 (d, 1H), 7.92-7.42 (m, 5H), 3.78-3.38 (m, 7H), 1.96 (m, 2H), 1.55 (m, 2H), 1.10 (t, 3H)

30

50

5

Example 3774-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxvethoxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

10 Treatment of N-Boc-4-hydroxylpiperidine with sodium hydride and chloroethyl
5 ethyl ether gave N-Boc-4-(2'-ethoxyl-ethoxy)-piperidine, which was treated with 4M HCl
in dioxane to give 4-(2'-ethoxyl-ethoxy)-piperidine.

15 The title compound was prepared as described for Example 367 substituting 4-(2'-ethoxyl-ethoxy)-piperidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, followed by treatment with 1M HCl ether.

10 MS (APCI+) m/z 550 (M+H)⁺;
20 ¹H NMR (300 MHz, DMSO-d₆) δ 10.10 (bs, 1H), 8.94 (s, 1H), 8.41 (s, 1H), 8.23 (d, 1H),
7.95-7.45 (m, 5H), 7.39 (bs, 1H), 4.15 (m, 3H), 3.70-3.30 (m, 6H), 1.94 (m, 3H), 1.50 (m, 3H), 1.08 (t, 3H)

25

Example 3784-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrapyranyloxyethyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

30 4-(2'-Hydroxylethyl)-piperidine was treated with triethylamine and Boc-anhydride in THF at room temperature. This crude product was treated with mesyl chloride and
20 triethylamine in dichloromethane to give the mesylate. This mesylate was then treated with sodium tetrahydro-4H-pyran-4-oxide (Example 372), followed by deprotection with 4M HCl in dioxane to give 4-(2'-(4''-azacyclohexyl)-ethoxy)-tetrahydro-4H-pyran.

35 The title compound was prepared as described for Example 367 substituting 4-(2'-(4''-azacyclohexyl)-ethoxy)-tetrahydro-4H-pyran for (1S,4S)-2-aza-5-oxa-
40 bicyclo[2.2.1]heptane, followed by treatment with 1M HCl ether.

25 MS (APCI+) m/z 590 (M+H)⁺;
45 ¹H NMR (300 MHz, DMSO-d₆) δ 10.10 (bs, 1H), 8.79 (s, 1H), 8.22 (s, 1H), 8.18 (d, 1H),
7.70-7.40 (m, 5H), 4.42 (m, 2H), 3.63 (m, 2H), 3.34 (m, 3H), 3.19 (m, 2H), 3.01 (m, 2H),
1.70 (m, 5H), 1.33 (m, 2H), 1.23 (m, 2H), 1.08 (m, 2H)

30

50

5

Example 3794-amino-5-(3-bromophenyl)-7-(6-(3-(R)-tetrahydrofuranloxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

10

Prepared as described for Example 369; substituting (R)-3-hydroxytetrahydrofuran
5 for benzyl alcohol.

15

MS (APCI+) m/z 465 (M+H)⁺;

20

¹H NMR (300 MHz, DMSO-d₆) δ 10.08 (bs, 1H), 8.93 (s, 1H), 8.52 (d, 1H), 8.51 (s, 1H),
25 7.98-7.40 (m, 6H), 5.80 (m, 1H), 4.05-3.78 (m, 4H), 2.36 (m, 1H), 2.15 (m, 1H)

10

Example 3804-amino-5-(3-bromophenyl)-7-(6-(3-(S)-tetrahydrofuranloxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

20

Prepared as described for Example 369; substituting (S)-3-hydroxytetrahydrofuran
25 for benzyl alcohol.

15

MS (APCI+) m/z 465 (M+H)⁺;

20

¹H NMR (300 MHz, DMSO-d₆) δ 10.08 (bs, 1H), 8.93 (s, 1H), 8.52 (d, 1H), 8.51 (s, 1H),
25 7.98-7.40 (m, 6H), 5.80 (m, 1H), 4.05-3.78 (m, 4H), 2.36 (m, 1H), 2.15 (m, 1H)

30

10

Example 3814-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

20

The title compound was prepared as described for Example 367 substituting anti-3-ethoxy-4-hydroxypyrrolidine (Chemical and Pharmaceutical Bulletin, 41, 1993, 132,
35 Okada, T.) for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, followed by treatment with 1M
40 HCl ether.

25

MS (APCI+) m/z 508 (M+H)⁺;

30

¹H NMR (300 MHz, DMSO-d₆) δ 10.12 (bs, 1H), 8.89 (s, 1H), 8.38 (d, 1H), 8.28 (s, 1H),
35 7.90-7.40 (m, 5H), 4.40-3.40 (m, 9H), 1.10 (t, 3H)

40

Example 382

50

5

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

- 10 Treatment of anti-N-Boc-3-ethoxy-4-hydroxypyrrolidine (Chemical and Pharmaceutical Bulletin, 41, 1993, 132, Okada, T.) with triphenylphosphine, 4-nitrobenzoic acid and diethyl azodicarboxylate in THF at 0°C to room temperature gave a syn-N-Boc-3-ethoxy-4-(4'-nitrophenylcarbonyloxy)pyrrolidine. This was then hydrolyzed with sodium hydroxide in methanol to give syn-N-Boc-3-ethoxy-4-hydroxypyrrolidine, which was subsequently deprotected with 4M HCl in dioxane to give syn-3-ethoxy-4-hydroxypyrrolidine.
- 15 10 The title compound was prepared as described for Example 367 substituting syn-3-ethoxy-4-hydroxypyrrolidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, followed by treatment with 1M HCl ether.
- 20 MS (ESI+) m/z 508 (M+H)⁺;
- 25 ¹H NMR (300 MHz, DMSO-d₆) δ 10.17 (bs, 1H), 8.91 (s, 1H), 8.38 (d, 1H), 8.28 (s, 1H), 7.91-7.79 (m, 2H), 7.67-7.49 (m, 4H), 4.80-3.50 (m, 9H), 1.39 (t, 3H)

Example 383

- 30 4-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine
- 20 The title compound was prepared as described for Example 370 substituting anti-3-ethoxy-4-hydroxypyrrolidine (Chemical and Pharmaceutical Bulletin, 41, 1993, 132, Okada, T.) for 4-methoxypiperidine, followed by treatment with 1M HCl ether.
- 35 MS (ESI+) m/z 507 (M+H)⁺;
- 40 ¹H NMR (300 MHz, DMSO-d₆) δ 10.00 (bs, 1H), 9.03 (s, 1H), 8.87 (s, 1H), 8.74 (d, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.80 (m, 1H), 7.59 (m, 2H), 7.36 (m, 1H), 7.11 (m, 1H), 4.40-3.00 (m, 9H), 1.10 (t, 3H)

Example 384

- 45 4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine
- 50

5

10

15

20

Treatment of anti-N-Boc-3-ethoxy-4-hydroxypyrrolidine (Chemical and Pharmaceutical Bulletin, 41, 1993, 132, Okada, T.) with sodium hydride and ethyl iodide in anhydrous DMF gave anti-N-Boc-3,4-diethoxypyrrolidine, which was subsequently deprotected with 4M HCl in dioxane to give anti-3,4-diethoxypyrrolidine.

5 The title compound was prepared as described for Example 367 substituting anti-3,4-diethoxypyrrolidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, followed by treatment with 1M HCl ether.

MS (FAB+) m/z 536 (M+H)⁺;
¹H NMR (300 MHz, DMSO-d₆) δ 10.18 (bs, 1H), 8.82 (s, 1H), 8.39 (d, 1H), 8.34 (s, 1H),
10 7.90 (m, 2H), 7.70-7.46 (m, 4H), 4.25 (m, 2H), 3.84 (m, 4H), 3.67 (m, 4H), 1.2 (t, 6H)

Example 385

25

4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

30

15 The title compound was prepared as described for Example 370 substituting anti-3,4-diethoxypyrrolidine (Example 382) for 4-methoxypiperidine, followed by treatment with 1M HCl ether.

MS (ESI+) m/z 535 (M+H)⁺;
¹H NMR (300 MHz, DMSO-d₆) δ 10.00 (bs, 1H), 9.03 (m, 1H), 8.87 (s, 1H), 8.71 (m, 1H),
20 8.22 (s, 1H), 7.95 (m, 1H), 7.80 (m, 1H), 7.58 (m, 2H), 7.35 (bs, 1H), 7.09 (m, 1H), 4.25-
35 3.20 (m, 10H), 1.12 (t, 6H)

Example 386

40

4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

45

Treatment of N-benzyl-3-pyrrolidine with osmium tetroxide and N-methyl-morpholine-N-oxide in THF gave syn-N-Boc-3,4-dihydroxypyrrolidine, which was then treated with sodium hydride (5 eq.) and ethyl iodide (5 eq) in DMF to give syn-N-Boc-3,4-diethoxypyrrolidine. This was debenzylated under pressure in H₂ atmosphere to afford
30 syn-3,4-diethoxypyrrolidine.

50

5

The title compound was prepared as described for Example 370 substituting *syn*-3,4-diethoxypyrrolidine for 4-methoxypiperidine, followed by treatment with 1M HCl ether.

10

MS (ESI+) m/z 535 (M+H)⁺;

15

¹H NMR (300 MHz, DMSO-d₆) δ 10.03 (bs, 1H), 9.03 (m, 1H), 8.89 (s, 1H), 8.74 (m, 1H), 8.25 (s, 1H), 7.95 (m, 1H), 7.62 (m, 1H), 7.60 (m, 2H), 7.39 (bs, 1H), 7.11 (m, 1H), 4.30-3.40 (m, 10H), 1.16 (t, 6H)

Example 387

20

4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

25

The title compound was prepared as described for Example 367 substituting *syn*-3,4-diethoxypyrrolidine (prepared in Example 384) for (1S,4S)-2-aza-5-oxabicyclo[2.2.1]heptane, followed by treatment with 1M HCl ether.

30

MS (ESI+) m/z 536.1 (M+H)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 10.13 (bs, 1H), 8.87 (s, 1H), 8.35 (d, 1H), 8.28 (s, 1H), 7.82 (m, 2H), 7.63-7.40 (m, 4H), 4.40-3.40 (m, 10H), 1.16 (t, 6H)

Example 388

35

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

40

The title compound was prepared as described for Example 370 substituting *syn*-3-ethoxy-4-hydroxypyrrolidine (prepared as in Example 382) for 4-methoxypiperidine, followed by treatment with 1M HCl ether.

45

MS (ESI+) m/z 507 (M+H)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 10.00 (bs, 1H), 9.02 (m, 1H), 8.88 (s, 1H), 8.72 (m, 1H), 8.22 (s, 1H), 7.97 (m, 1H), 7.81 (m, 1H), 7.60 (m, 2H), 7.39 (bs, 1H), 7.17 (m, 1H), 4.40-3.40 (m, 9H), 1.17 (t, 3H)

30

Example 389

50

5

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

10

Syn-N-benzyl-3-hydroxy-4-(t-butylcarbonylamino)pyrrolidine was made by Sharpless method (JACS 120 1998 1215. Sharpless, K.B.: Tetrahedron asymmetry 5(7) 1994 1333, Saigo K.). This was debenzylated under H₂ to give syn-3-hydroxy-4-(t-butylcarbonylamino)pyrrolidine.

15

The title compound was prepared as described for Example 367 substituting syn-3-hydroxy-4-(t-butylcarbonylamino)pyrrolidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, followed by treatment with 4M HCl dioxane.

20

MS (ESI+) m/z 479.2 (M+H)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 10.07 (bs, 1H), 8.94 (s, 1H), 8.59 (bs, 2H), 8.35 (m, 2H), 7.85 (m, 2H), 7.70-7.30 (m, 4H), 4.70-3.20 (m, 9H)

25

Example 390 4-amino-5-(3-bromophenyl)-7-(6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

30

The title compound was prepared as described for Example 370 substituting syn-3-hydroxy-4-(t-butylcarbonylamino)pyrrolidine (prepared in Example 389) for 4-methoxypiperidine, followed by treatment with 4M HCl dioxane.

MS (APCI+) m/z 478 (M+H)⁺;

35

¹H NMR (300 MHz, DMSO-d₆) δ 10.07 (bs, 1H), 9.08 (m, 1H), 8.88 (s, 1H), 8.64 (m, 3H), 8.21 (s, 1H), 7.97 (s, 1H), 7.82 (m, 1H), 7.60 (m, 2H), 7.36 (m, 1H), 7.03 (m, 1H), 4.65-3.65 (m, 9H)

40

Example 391

4-amino-5-(2-pyridyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

45

Prepared according to the procedure of Example 392, except substituting 5-acetyl-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)pyridine for 5-acetyl-2-morpholinylpyridine, and 3-pyridinecarboxaldehyde for 2,3-dichlorobenzaldehyde. The treatment with HCl/ethanol to form the hydrochloride salt was omitted, and the free base was obtained instead. IR

50

5

(MIC) 3500, 3310, 3100, 2982, 1605, 1580, 1555, 1512, 1351, 1238, 1100cm⁻¹; MS m/z 442 (M+H)⁺

10

Example 392

- 5 4-amino-5-(2,3-dichlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine
 4-(2,3-Dichlorophenyl)-3-cyano-6-(6-morpholinyl-3-pyridyl)pyridine-2-amine
15 (0.47 g) and ammonium sulfate (20 mg) was dissolved in triethylorthoformate (25 ml) and
 heated to reflux for about 6.5 hours. The reaction mixture was cooled to room temperature,
 and a 2 M solution of ammonia in ethanol (50 ml) was added. The reaction was stirred at
20 room temperature for about 18 hours, then heated to reflux for about 6 hours, and then
 cooled again to room temperature. The solvents were removed under vacuum. The residue
 was purified by flash chromatography eluting with 5% of 19:1 ethanol:ammonium
25 hydroxide in ethyl acetate, and then converted to the hydrochloride salt by treatment with
 HCl/EtOH, followed by removal of solvent and tituration with ether to give the title
 compound.

IR (MIC) 3355, 2980, 1644, 1602, 1437, 1369, 1250cm⁻¹;
MS m/z 453 (M+H)⁺

30

Step a 4-(2,3-dichlorophenyl)-3-cyano-6-(6-morpholinyl-3-pyridyl)pyridine-2-amine

- 20 Malononitrile (0.33 g) and 2,3-dichlorobenzaldehyde (0.88 g) were dissolved in
 1,2-dichloroethane, and 1-2 drops of triethylamine were added. The reaction was stirred at
 room temperature for about 2.5 hours, then 5-acetyl-2-morpholinylpyridine (0.62 g) and
 ammonium acetate (2.31 g) were added. The reaction was heated to reflux for about 5
 hours, then cooled to room temperature. The reaction mixture was purified by flash
40 chromatography eluting with 30% EtOAc/Hexanes.

Example 393

- 45 4-amino-5-(2-pyridyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine
 Prepared according to the procedure of Example 392 except substituting 3-
30 pyridinecarboxaldehyde for 2,3-dichlorobenzaldehyde.

50

5

IR (MIC) 3050, 1650, 1603, 1540, 1440, 1375, 1252cm⁻¹;
MS m/z 386 (M+H)⁺

10

Example 3945 4-amino-5-(2-ethoxyphenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

15

Prepared according to the procedure of Example 392, except substituting 5-acetyl-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)pyridine for 5-acetyl-2-morpholinylpyridine, and 2-ethoxybenzaldehyde for 2,3-dichlorobenzaldehyde. The treatment with HCl/ethanol to form the hydrochloride salt was omitted, and the free base was obtained instead.

10

IR (MIC) 3480, 3060, 1738, 1640, 1600, 1560, 1537, 1500, 1345, 1230, 1220, 1100cm⁻¹;
MS m/z 485 (M+H)⁺

25

Example 39515 4-amino-5-(2-bromo-5-ethoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

30

Prepared according to the procedure of Example 392, except substituting 2-methoxy-5-bromobenzaldehyde for 2,3-dichlorobenzaldehyde.

IR (MIC) 3440, 2975, 1642, 1600, 1490, 1440, 1370, 1250cm⁻¹;
MS m/z 493 (M+H)⁺

35

Example 3964-amino-5-(2,5-dichlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

4-(2,5-dichlorophenyl)-3-cyano-6-(6-morpholinyl-3-pyridyl)pyridine-2-amine

40

25 (0.28 g) and ammonium sulfate (10 mg) were dissolved in triethylorthoformate (10 ml) and heated to reflux for about 4 hours. The reaction mixture was cooled to room temperature, and a 2 M solution of ammonia in ethanol (20 ml) was added. The reaction was stirred at room temperature for about 18 hours, then a solution of 1 M sodium methoxide in methanol (5 ml) was added. The reaction was heated to reflux for about 2.5 hours, and then cooled again to room temperature. The reaction mixture was neutralized

50

5

10

15

20

30

40

50

with a solution of 1 N aqueous HCl (5 ml) and the solvents were removed under vacuum. The residue was purified by flash chromatography eluting with 2.5% of 19:1 ethanol:ammonium hydroxide in ethyl acetate, and then converted to the hydrochloride salt by treatment with HCl/EtOH, followed by removal of solvent and tituration with ether to give the title compound.

IR (MIC) 3480, 3060, 1640, 1600, 1580, 1440, 1371, 1260, 1239cm⁻¹;

MS m/z 453.2 (M+H)⁺

The 4-(2,5-dichlorophenyl)-3-cyano-6-(6-morpholinyl-3-pyridyl)pyridine-2-amine was prepared following the conditions given under Example 392 except substituting 2,5-dichlorobenzaldehyde for 2,3-dichlorobenzaldehyde.

Example 397

4-amino-5-(2,5-dimethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared according to the procedure of Example 396, except substituting 2,5-

dimethylbenzaldehyde for 2,5-dichlorobenzaldehyde.

IR (MIC) 3420, 2910, 1640, 1600, 1580, 1240cm⁻¹;

MS m/z 413.2 (M+H)⁺

Example 399

4-amino-5-(3-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared according to the procedure of Example 396, except substituting 3-

fluorobenzaldehyde for 2,5-dichlorobenzaldehyde.

IR (KBr) 3480, 1672, 1639, 1617, 1480, 1421, 1315, 1305cm⁻¹;

MS m/z 403 (M+H)⁺

25

Example 400

4-amino-5-(3-trifluoromethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared according to the procedure of Example 396, except substituting 3-

trifluoromethylbenzaldehyde for 2,5-dichlorobenzaldehyde.

IR (MIC) 3000, 1641, 1600, 1440, 1369, 1324, 1239, 1120cm⁻¹;

55

5

MS m/z 453 (M+H)⁺

10

Example 401

4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

5

Prepared according to the procedure of Example 327, substituting 3-fluoro-5-trifluoromethylbenzaldehyde for 3-bromobenzaldehyde.

15

mp: unmelted at 300°C;

MS (FAB)⁺ m/z calc'd for C₂₆H₂₃N₆O₂F₄: 527.1813, found 527.1810.

10

IR (cm⁻¹): 3314, 3081, 1580, 1558, 1515, 1428, 1357, 1329, 1238, 1139, 1106.

20

Example 402

4-amino-5-(3,5-dichlorophenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

25

Prepared according to the procedure of Example 327, except substituting 3,5-dichlorobenzaldehyde for 3-bromobenzaldehyde.

30

mp: unmelted at 300°C;

MS (FAB)⁺ m/z calc'd for C₂₃H₂₃N₆O₂Cl₂: 509.1254, found: 509.1246

IR (cm⁻¹): 3487, 3299, 3065, 1578, 1556, 1515, 1431, 1354, 1238, 1104.

20

35

Example 403

4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxa-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

40

Prepared according to the procedure of Example 367, except substituting 1,5-dioxa-9-azaspiro[5.5]undecane for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane.

mp: δ 190°C;

MS (FAB)⁺ m/z calc'd for C₂₃H₂₃N₆O₂³¹Br: 536.1233, found: 536.1233.

45

IR (cm⁻¹): 3471, 3297, 3059, 2961, 1579, 1562, 1461, 1407, 1354, 1236, 1104.

30

Example 404

50

5

4-amino-5-(4-bromo-2-thienyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

10

Prepared according to the procedure of Example 327, substituting 4-bromothiophene-2-carboxaldehyde for 3-bromobenzaldehyde.

15

mp: δ 245°C;

MS (FAB)⁺ m/z calc'd for C₂₃H₂₂N₆O₂S⁷⁹Br: 525.0703, found: 525.0699.

IR (cm⁻¹): 3477, 3296, 3094, 1603, 1579, 1556, 1511, 1428, 1352, 1239, 1104.

Example 405

20

10 4-amino-5-(3-bromophenyl)-7-(6-(4-tertbutyl)piperidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine

25

Prepared by the method of Example 367, substituting 4-tertbutylpiperidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane.

mp: δ > 270°C;

15 MS (FAB)⁺ m/z calc'd for C₂₆H₂₉N, ⁷⁹Br: 520.1647, found: 520.1652.

IR (cm⁻¹): 3474, 3298, 3085, 2952, 1578, 1553, 1461, 1405, 1351, 1254, 1191, 1159.

30

Example 406

35

20 4-amino-5-(3-bromophenyl)-7-(6-(4-N-formyl)piperidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine

40

35 2-Amino-4-(3-bromophenyl)-3-cyano-6-(6-chloro-3-pyridazinyl)pyridine (310mg), prepared in Example 367, and 1,3-propylenedioxypiperidine (354mg) were dissolved into DMSO (2.5ml) and stirred 48 hours. The reaction mixture was partitioned between 0.4M pH7 aqueous potassium phosphate buffer and worked up as usual. The intermediate was suspended in formamide (15ml) and o-dichlorobenzene (7ml) and heated at 200°C for 2.5h. The reaction mixture was partitioned between salt water and dichlormethane, and the organic phase was separated, filtered through celite, and worked up as usual. Chromatographed (MeOH/EtOAc/CH₂Cl₂).

45

mp: δ 190°C;

30 MS (FAB)⁺ m/z calc'd for C₂₃H₂₂N₆O, ⁷⁹Br: 505.1094, found: 505.1095.

50

5

IR (cm^{-1}): 3472, 3299, 1654, 1578, 1555, 1478, 1418, 1354, 1225.

10

Example 407

4-amino-5-(3-bromo-2-thienyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

15

Prepared by the method of Example 327, substituting 3-bromothiophene-2-carboxaldehyde for 3-bromobenzaldehyde.

20

mp: δ 230°C;

MS (FAB) $^-$ m/z calc'd for $C_{23}H_{22}N_6O_2S^{79}\text{Br}$: 527.0688, found: 527.0692.

IR (cm^{-1}): 3472, 3297, 3091, 1611, 1581, 1557, 1519, 1428, 1351, 1334, 1229, 1112.

25

Example 408

4-amino-5-(3-cyanophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine

30

A formamide complex of Example 134 (762mg), $Zn(\text{CN})_2$ (94mg), and $Pd(PPh_3)_4$ (173mg) were heated in DMF (5ml) at 105°C for 3h 40m. The reaction mixture was partitioned between CH_2Cl_2 and water and worked up as usual. Recrystallization of the crude solid from CHCl_3 gave the title compound.

35

mp: δ 290°C;

MS (FAB) $^-$ m/z calc'd for $C_{22}H_{20}N_6O$: 410.1724, found: 410.1722.

IR (cm^{-1}): 3482, 3313, 2232, 1588, 1542, 1507, 1357, 1240.

40

Example 409

4-amino-5-(3-Bromophenyl)-7-(6-(S-O-ethyl-2-hydroxymethylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

45

Prepared by the method of Example 367, substituting (S)-O-ethyl-2-hydroxymethylpyrrolidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane.

mp: δ 180°C;

MS (FAB) $^-$ m/z calc'd for $C_{24}H_{22}N_6O_3^{79}\text{Br}$: 508.1283, found: 508.1285.

IR (cm^{-1}) of salt: 3438, 3302, 2974, 1637, 1609, 1588, 1554, 1440, 1374, 1111.

50

5

10

15

20

25

30

35

40

45

50

Step a. (S)-O-ethyl-2-hydroxymethylpyrrolidine

A suspension of (S)-N-tertbutyloxycarbonyl-2-hydroxymethylpyrrolidine (1006mg) and crushed NaOH (800mg) in DMSO (20ml) was treated with ethyl iodide (560ml). After the suspension had been stirred for 45m, the reaction mixture was partitioned between 0.2M aq KH₂PO₄ and Et₂O, worked up as usual, and concentrated. A solution of the intermediate (1.04g) in MeOH (10ml) was treated with conc aq HCl (1.5ml) and stirred over the weekend. The reaction mixture was concentrated and partitioned between 3M aq K₂PO₄ and Et₂O, worked up as usual, and concentrated to give the desired amine

Example 4104-amino-5-(3-bromophenyl)-7-(6-((2S,3S)-2,3-dimethyl-1,4-dioxa-8-azaspiro[4.5]decane-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared by the method of Example 327, substituting (2S,3S)-2,3-dimethyl-1,4-dioxa-8-azaspiro[4.5]decane for 4,4-ethylenedioxypiperidine and using 1,2,4-trichlorobenzene as cosolvent with formamide at 200°C in the final cyclization.
mp: δ >235°C; MS (FAB)⁺ m/z calc'd for C₂₆H₂₇N₃O₂³¹Br: 550.1389, found: 550.1374.
IR (cm⁻¹): 3477, 3046, 2968, 1578, 1559, 1460, 1410, 1353, 1251, 1113.

20 410a. 4,4-(1S,2S-dimethylethanedioxy)piperidine

N-tertbutyloxycarbonylpiperidi-N-4-one (2.59g), (2S,3S)-butanediol (1.464g), and a catalytic amount of p-toluenesulphonic acid were dissolved into benzene (25ml) within a flask fitted with a Dean-Stark trap and condenser, and refluxed 1 day. The reaction mixture was partitioned between aq NaHCO₃ and ether, and worked up as usual. Chromatographed (CH₂CN/CH₂Cl₂). This intermediate (3.78g) was dissolved into CH₂Cl₂ (10ml) and treated with TFA (3ml). After 90m more TFA (0.5ml) was added, and after another 90min the reaction mixture was concentrated, then conc'd from CHCl₃, then from toluene. The intermediate, 6-acetyl-3-chloropyridazine (2.03g), and diisopropylethylamine (9.75ml) were dissolved into methanol (55ml) and heated at 55°C for 2d. The reaction mixture was added to Et₂O and 1M pH7 aq potassium phosphate buffer and worked up as usual. Purified by column chromatography (EtOAc/Hexanes).

5

10

Example 4114-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-1,2-dioxycyclopentyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

5 Prepared by the method of Example 410 (A-312378), substituting cis-1,2-dihydroxycyclopentane for (2S,3S)-butanediol.

15

mp: unmelted at 300°C;

MS (FAB)⁺ m/z calc'd for C₂₁H₂₁N₃O₂⁸¹Br: 562.1389, found: 562.1382.

IR (cm⁻¹): 3478, 3081, 2959, 1578, 1560, 1460, 1406, 1351, 1246, 1109.

10

20

Example 4124-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-1-oxa-4,8-diazaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

25 4-Acetyl-1-oxa-4,8-diazaspiro[4.5]decane (341mg) was dissolved into CH₂Cl₂ (0.5ml) and
15 treated with TFA (1ml). After 20m the reaction mixture was concentrated. The intermediate,
potassium carbonate (552mg), and 4-amino-5-(3-bromophenyl)-7-(6-chloropyridaz-3-
30 yl)pyrido[2,3-d]pyrimidine (165mg), prepared in Example 367, were suspended in DMSO (2ml)
and heated 6h at 120°C. The reaction mixture was partitioned between brine and CH₂Cl₂ and
worked up as usual. Purification by chromatography (CH₃OH/CH₃CN/CH₂Cl₂) provided the title
20 compound..

35 mp: dec 260°C (sweats and turns deep brown 220°C); MS (FAB)⁺ m/z calc'd for C₂₆H₂₆N₃O₂⁸¹Br:
563.1342, found: 563.1329.

IR (cm⁻¹): 3487, 3308, 1626, 1578, 1553, 1461, 1416, 1353, 1254, 1073.

40

25 412a.

45 N-tertbutyloxycarbonyl-4-oxopiperidine (996mg) and 2-aminoethanol (320ml) were
dissolved into ethanol (5ml). After 4h, the reaction mixture was concentrated, and the residue
30 dissolved into CH₂Cl₂ (8ml) and pyridine (2ml). Acetyl chloride (360ml) was added and the
mixture was stirred overnight. More acetyl chloride (350ml) was added then and the same
amount 2h later. After 15m more, the reaction mixture was quenched with aq NaHCO₃, and

50

5

worked up as usual but with NaHCO₃ and NaCl in each aqueous wash. This intermediate was purified by chromatography (EtOAc/Hexanes).

10

Example 413

5 4-amino-5-(3-bromophenyl)-7-(6-((2R,3R)-2,3-bis(methoxymethyl)-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

15

Prepared following the procedure according to Example 412 (A-314908), substituting (2R,3R)-2,3-bis(methoxymethyl)-1,4-dioxa-8-azaspiro[4.5]decan for 412a.

mp: δ >130°C; MS (FAB)⁺ m/z calc'd for C₂₈H₃₁N₃O₃⁷⁹Br: 608.1615, found: 608.1614.

20

10 IR (cm⁻¹): 3486, 3304, 2928, 1578, 1554, 1461, 1407, 1352, 1235, 1106.

Example 414

25 4-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-3,4-dioxy-oxacyclopentyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

15

Prepared following the procedure of Example 412 (A-314908), substituting 4,4-(cis-3,4-dioxy-oxacyclopentane)piperidine for 412a.

mp: δ 280°C; MS (FAB)⁺ m/z calc'd for C₂₆H₂₅N₃O₃⁷⁹Br: 562.1202, found: 562.1209.

30

IR (cm⁻¹): 3475, 3293, 3094, 1577, 1559, 1461, 1410, 1355, 1229, 1111.

20

Example 415

35

4-amino-5-(3-bromophenyl)-7-(6-(3-methoxy-1,5-dioxa-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared following the procedure of Example 412 (A-314908), substituting 3-methoxy-1,5-dioxa-9-azaspiro[5.5]undecane for 412a.

40

25 mp: δ 275°C; MS (FAB)⁺ m/z calc'd for C₂₆H₂₅N₃O₃⁷⁹Br: 564.1359, found: 564.1354.

IR (cm⁻¹): 3478, 3293, 3070, 1574, 1564, 1462, 1407, 1349, 1227, 1147, 1101.

45

Example 416

30 4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxa-3-hydroxymethyl-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

50

5

Prepared following the procedure of Example 412, substituting 1,5-dioxa-3-hydroxymethyl-9-azaspiro[5.5]undecane for 412a, and adding butanol during the work-up.
mp: unmelted at 300°C (sweats/shrivels >270°C); MS (ESI)⁻ m/z: 564/566.
IR (cm⁻¹): 3475, 3302, 1578, 1554, 1462, 1409, 1354, 1237, 1146, 1100.

10

5

Example 417

15

4-amino-5-(3-bromophenyl)-7-(6-(1,7,14-trioxa-11-azadispiro[4.2.5.2]pentadecan-11-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

20

Prepared following the procedure of Example 412 (A-314908), substituting 1,7,14-trioxa-11-azadispiro[4.2.5.2]pentadecane for 412a.
mp: unmelted at 300°C; MS (ESI)⁻ m/z: 590/592.
IR (cm⁻¹): 3476, 3295, 3087, 2968, 1577, 1562, 1465, 1419, 1356, 1149, 1099.

25

Example 4184-amino-5-(4-tetrahydropyranyl)-7-(4,4-ethylenedioxybiperidinyl)pyrido[2,3-d]pyrimidine

30

Prepared following the procedure according to Example 327, substituting 1,1-dicyano-3-(4-tetrahydropyranyl)ethene from Example 292 for 3-bromobenzaldehyde, and 6-acetyl-3-chloropyridazine for 5-acetyl-2-chloropyridine at room temperature rather than reflux.
mp: unmelted at 300°C; MS (FAB)⁻ m/z calc'd for C₂₃H₂₇N₃O₃: 450.2254, found: 450.2266.
IR (cm⁻¹): 3544, 3304, 2938, 1579, 1557, 1468, 1415, 1355, 1240, 1104.

35

Example 4194-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

40

Prepared as described for Example 359; substituting 4-aminomorpholine for ethoxylamine hydrochloride.
MS (DCI/NH₃) m/z 559 (M+H)⁺;
IR (cm⁻¹): 1643, 1602, 1557.

45

30

Example 420

50

5

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

10 Prepared as described for Example 419 except substituting 1-amino-4-N-methylpiperazine for 1-aminomorpholine.

5 MS (DCI) m/e 572 (M+H⁺);
IR 1647, 1602, 1559.

15

Example 421

4-amino-5-(3-bromophenyl)-7-(6-(4-(1,2,4-triazol-1-yl)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

20 Prepared as described for Example 419 except substituting 4-amino-1,2,4-triazole for 1-aminomorpholine
MS (DCI) m/e 541 (M+H⁺);
IR 1602, 1580.

15

Example 422

4-amino-5-(3-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

30 The title compound was prepared following the procedure of Example 396 except substituting 3-indolylcarboxaldehyde for 2,5-dichlorobenzaldehyde.

20 MS (DCI), m/z 424.
35 H¹ NMR (DMSO-d₆) d, 11.81 (s, 1H), 9.05 (d, 1H), 8.5 (s, 1H), 8.45 (dd, 1H), 7.84 (s, 2H), 7.55 (d, 1H), 7.40 (d, 1H), 7.25 (t, 1H), 7.10 (t, 1H), 6.58 (d, 1H), 3.72 (m, 4H), 3.6 (m, 4H).

40

25

Example 423

4-amino-5-(5-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

45 The title compound was prepared following the procedure of Example 422 except substituting 5-indolylcarboxaldehyde for 3-indolylcarboxaldehyde, which was prepared according to the procedure of Moyer et. al. Journal of Organic Chemistry, 51, 5106-5110.
30 1986.

50

5

MS (DCI). m/z 452.

IR (mic. cm⁻¹) 3448, 1557, 1503, 1234, 943.

10

Example 424

5 4-amino-5-(3-bromophenyl)-7-(6-(4-ethylpiperidinylcarboxylate)-3-pyridyl)pyrido[2,3-d]pyrimidine

15

Prepared following the procedures of Example 327 except substituting ethyl 4-piperidinecarboxylate for 4,4-ethenedioxypiperidine.

MS (DCI) m/e 533 (M+H)⁺;

10 IR (mic.,cm⁻¹) 1604, 1592, 1560

20

Example 425

4-amino-5-(3-bromophenyl)-7-(2-phenylmethyl-3(2H)-pyridazinone-6-yl)pyrido[2,3-d]pyrimidine

25

15 step a 3-acetyl-6-hydroxypyridazine

A solution of 3-acetyl-6-chloropyridazine (prepared in Example 246 step b)(6.0 g, 38.4 mmol) and aq. 3N HCl (70 mmol) in THF (100 mL) was heated at 60°C for 4 h, cooled to ambient temperature, concentrated and chromatographed on silica gel (30% EtOAc-hexane) to obtain the desired compound (3.3 g, 62%). ¹H NMR (CDCl₃, 300 MHz) δ 12.42 (broad s, 1H), 7.98 (d, J=9.0 Hz, 1H), 7.02 (d, J=9.0 Hz, 1H), 2.58 (s, 3H); MS m/z (DCI) 139 (M+H)⁺.

35

step b 6-acetyl-2-phenylmethyl-3(2H)-pyridazinone

A solution of 3-acetyl-6-hydroxypyridazine (2.9 g, 21.0 mmol), benzyl bromide (2.8 mL, 23.0 mmol) and KOH (1.3 g, 23.0 mmol) in DMF (45 mL) was stirred at ambient temperature for 15 h. The mixture was diluted with EtOAc and washed twice with water. Aqueous layer was extracted with EtOAc and combined organic fractions concentrated and chromatographed (10-25%EtOAc-hexane) to obtain of the desired 6-acetyl-2-phenylmethyl-3(2H)-pyridazinone (3.6 g, 75%) as an oil. ¹H NMR (CDCl₃, 300

50

5

MHz) δ 7.80 (d, J=9.2 Hz, 1H), 7.48-7.27 (m, 5H), 6.90 (d, J=9.2 Hz, 1H), 5.38 (s, 2H), 2.51 (s, 3H); MS m/z (DCI) 229 (M+H)⁺.

10

The title compound was prepared as described in Example 327 except substituting 6-acetyl-2-phenylmethyl-3(2H)-pyridazinone for 3-acetyl-(4,4-

5 ethylenedioxypiperidinyl)pyridine

MS (DCI) m/e 485 (M+H⁺);

15

IR 1640, 1618, 1560.

Example 426

10 4-amino-5-(3-bromophenyl)-7-(6-(4-(morpholinylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

20

The title compound was prepared following the procedure of Example 424 except substituting 3-acetyl-6-(4-N-morpholinylcarboxamide)piperidinyl)pyridine for ethyl-4-piperidinecarboxylate derivative.

25

15 MS (ESI+), m/z 575 (M+H)⁺;

IR (MIC); cm⁻¹, 3486, 1557, 1211, 933.

30

3-acetyl-6-(4-N-morpholinylcarboxamide)piperidinyl)pyridine:

2-chloro-5-acetylpyridine (6g) and ethyl isonipeptate (6.1g) was refluxed in 20 ethanol. The volatiles were evaporated to leave 2-(1'-ethyl isonipeptate)-4-acetylpyridine. This material was treated with aqueous lithium hydroxide, followed by acidification and filtration. The resulting acid (1.5 g) was treated with morpholine (2.4 g), hydroxybenzotriazole (1.3g) and 1-(3-Dimethylaminopropyl)-3-carbodiimide, to afford the 35 desired compound .

40

25 MS (DCI) m/z, 318 (M+H)⁺.

Example 427

45 4-amino-5-(3-bromophenyl)-7-(6-(4-(N-morpholinylaminocarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

50

5

Prepared following the procedure of Example 426 except substituting 4-aminomorpholine for morpholine.

10

MS (ESI) m/z 589 (M+H)⁺;
IR (cm⁻¹) 3490, 1557, 1351, 1111.

5

15

Example 428

4-amino-5-(3-bromophenyl)-7-(6-(4-(N,N-dimethylaminocarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

20

Prepared following the procedure of Example 426 except substituting dimethylamine for morpholine.

25

MS (ESI) m/z 532 (M+H)⁺;
H¹ NMR (300 MHz; DMSO-d₆, δ 9.05 (d, 1H), 8.52 (s, 1H), 8.44 (dd, 1H), 7.85 (s, 2H),
7.78 (dt, 1H), 7.55 (s, 1H), 6.99 (d, 1H), 4.49 (d, 2H), 3.09 (s, 2H), 3.00 (m, 3H), 2.80 (s,
3H), 1.7 (m, 2H), 1.54 (m, 2H).

15

Example 429

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methyl-N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

30

Prepared following the procedure of Example 426 except substituting N-methyl-N-methoxyethylamine for morpholine..

35

MS (ESI+) m/z 576, (M+H)⁺;
IR (mic, cm⁻¹) 3489, 1555, 1118, 936.

40

25

Example 430

4-amino-5-(4-quinolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

45

Prepared following the procedure of 392, substituting 4-quinolinecarboxaldehyde for 2,3-dichlorobenzaldehyde.

MS (ESI+). m/z 436 (M+H)⁺;

IR (mic., cm⁻¹) 3488, 1580, 1557, 1227, 936.

50

5

Example 431

10 4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methoxethylcarboxamide)pipridinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

15 Prepared following the procedure of Example 426, except substituting N-methoxyethylamine for morpholine...
MS (ESI+) M/z 564, (M+H)⁺;
IR (cm⁻¹) 3310, 1560, 1210, 954.

20

Example 432

25 4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxymethylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

30 Prepared as described for Example 370 except substituting 4-hydroxypiperidin-4-ylmagnesium bromide for 4-methoxypiperidine, which was prepared as follows:
35 ethyl isonipeptate (10g) was treated with lithium aluminum hydride (2.53g) in tetrahydrofuran for 36 hours.
MS. (ESI+) m/z 491 (M+H)⁺.

30

Example 433

20 4-amino-5-(2-bromophenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

35 Prepared as described for Example 370 except substituting 1,4-dioxa-8-azaspiro[4.5]decan-8-ylmagnesium bromide for 4-methoxypiperidine and substituting the dicyanostyrene derived from 2-bromobenzaldehyde instead of the 3-bromoderivative.

40 ¹H NMR (300 MHz, d₆-DMSO) δ 9.05 (d, 1H), 8.53 (s, 1H), 8.44 (dd, 1H), 7.91 (d, 1H), 7.83 (s, 1H), 7.66 (d, 2H), 7.56 (m, 1H), 7.04 (d, 1H), 3.93 (s, 3H), 3.77 (m, 4H), 1.67 (m, 4H);
45 MS (ESI) m/z 519/521 (M⁺+H, ⁷⁹Br/⁸¹Br).

50

Example 434

5

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

10

Prepared as described for Example 433 except substituting 4-hydroxypiperidine for
4,4-ethylenedioxypiperidine. IR (KBr pellet) ν_{max} 3485, 3298, 3198, 2938, 2848, 1600,
1574, 1557, 1357, 1225, 1024, 766 cm⁻¹;
MS (ESI) m/z 477/479 (M⁺+H, ⁷⁹Br/⁸¹Br).

15

Example 435

4-amino-5-(3-bromophenyl)-7-(6-(4-N-acetyl(piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

20

Prepared as described for Example 370 except substituting 1-acetyl piperazine for
4-methoxypiperidine.
¹H NMR (300 MHz, d₆-DMSO) δ 9.09 (d, 1H), 8.53 (s, 1H), 8.48 (dd, 1H), 7.86 (s, 1H),
7.85 (s, 1H), 7.78 (dt, 1H), 7.54 (m, 2H), 7.00 (d, 1H), 3.63-3.73 (m, 4H), 3.55-3.59 (m,
15 4H), 2.06 (s, 3H);
MS (ESI) m/z 504/506 (M⁺+H, ⁷⁹Br/⁸¹Br).

30

Example 436

4-amino-5-(3-bromophenyl)-7-(6-(4-cyanopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

20

Prepared as described for Example 370 except substituting 4-cyanopiperidine for
4-methoxypiperidine, which was prepared as follows: isonicotamide was heated in
POCl₃ at reflux for 2 hours and then was cooled to rt. Most of the POCl₃ was removed in
vacuo, and the remaining syrup was carefully quenched with ice. The melted aqueous
solution was extracted with CH₂Cl₂, and the combined organic extracts were dried over
25 Na₂SO₄. Removal of the solvent in vacuo afforded 4-cyanopiperidine as a grey-white semi-
solid.

40

¹H NMR (300 MHz, d₆-DMSO) δ 9.07 (d, 1H), 8.53 (s, 1H), 8.45 (dd, 1H), 7.85 (m, 2H),
7.76-7.80 (m, 1H), 7.52 (m, 2H), 7.02 (d, 1H), 3.95-4.02 (m, 2H), 3.46-3.55 (m, 2H), 3.17
45 (m, 1H), 1.94-1.99 (m, 2H), 1.74-1.80 (m, 2H);
30 MS (ESI) m/z 486/488 (M⁺+H, ⁷⁹Br/⁸¹Br).

50

5

Example 4374-amino-5-(3-bromophenyl)-7-(6-(4-N-(4-fluorophenyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

10 Prepared as described for Example 370 except substituting 1-(4-fluorophenyl)piperazine for 4-methoxypiperidine.

15 ^1H NMR (300 MHz, d_6 -DMSO) δ 9.10 (d, 1H), 8.53 (s, 1H), 8.48 (dd, 1H), 7.85 (m, 2H), 7.78 (dt, 1H), 7.55 (m, 2H), 7.00-7.11 (m, 5H), 3.81 (m, 4H), 3.21 (m, 4H);
MS (ESI) m/z 556/558 (M^++H , $^{79}\text{Br}/^{81}\text{Br}$).

10 20

Example 4384-amino-5-(4-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

25 Prepared as described for Example 370 except substituting morpholine for 4-methoxypiperidine and substituting the dicyanostyrene derived from 4-fluorobenzaldehyde
15 instead of the 3-bromoderivative.

30 ^1H NMR (300 MHz, d_6 -DMSO) δ 9.08 (d, 1H), 8.53 (s, 1H), 8.47 (dd, 1H), 7.83 (s, 1H), 7.65 (m, 2H), 7.44 (m, 2H), 6.99 (d, 1H), 3.59-3.73 (m, 8H);
MS (ESI) m/z 403 (M^++H).

20

Example 4404-amino-5-(3-bromophenyl)-7-(4-morpholinylbenzenesulfonamide)pyrido[2,3-d]pyrimidineStep a 3-acetyl-6-morpholinylbenzenesulphonamide

40 A solution of 4-acetylbenzenesulfonyl chloride in CH_2Cl_2 at -78° is treated with 2
25 equivalents of morpholine. The mixture is stirred at -78° for 1 hour and then warmed to rt
and stirred for 2 additional hours. After this time, the mixture is diluted with EtOAc and
is washed with water and brine. The solution is dried (Na_2SO_4) and concentrated in vacuo
45 to afford the desired 3-acetyl-6-morpholinylbenzenesulphonamide.

50

5

Step b 2-amino-3-cyano-4-(3-bromophenyl)-6-(6-morpholinylbenzenesulphonamide)pyridine

10

3-acetyl-6-morpholinylbenzenesulphonamide is then cyclized as described in example 244, using dicyanostyrene derived from 3-bromobenzaldehyde, to the desired 2-amino-3-cyano-4-(3-bromophenyl)-6-(6-morpholinylbenzenesulphonamide)pyridine

15

The material prepared in step b is converted to the title compound by cyclization with trisformamide using conditions described in Example 370.

20

¹H NMR (300 MHz, d₆-DMSO) δ 8.62 (s, 1H), 8.60 (d, 2H), 8.05 (s, 1H), 7.89-7.92 (m, 3H), 7.81 (dt, 1H), 7.53-7.63 (m, 2H), 3.65 (m, 4H), 2.94 (m, 4H); MS (ESI) m/z 526/528 (M⁺+H, ⁷⁹Br/⁸¹Br).

Example 441

25

4-amino-5-(3-bromophenyl)-7-(4-N-1,4-dioxa-8-azaspiro[4.5]decane-8-ylbenzenesulphonamide)pyrido[2.3-d]pyrimidine

15 Prepared as described for Example 440 except substituting 1,4-dioxa-8-azaspiro[4.5]decane for morpholine in step a.

30

¹H NMR (300 MHz, d₆-DMSO) δ 8.62 (s, 1H), 8.58 (d, 2H), 8.05 (s, 1H), 7.91-7.93 (m, 3H), 7.80 (dt, 1H), 7.53-7.63 (m, 2H), 3.80 (s, 4H), 3.06 (m, 4H), 1.69 (m, 4H); MS (ESI) m/z 582/584 (M⁺+H, ⁷⁹Br/⁸¹Br).

20

Example 442

35

4-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylbenzenesulphonamide)pyrido[2.3-d]pyrimidine

40

Prepared as described for Example 440 except substituting n-cyclopropylamine for morpholine in step a.

45

IR (KBr pellet) ν_{max} 3478, 3301, 3059, 2847, 2761, 2664, 1730, 1696, 1642, 1579, 1567, 1486, 1349, 1327, 1156, 1094, 887, 844, 828, 798 cm⁻¹; MS (ESI) 496/498 (M⁺+H, ⁷⁹Br/⁸¹Br).

30

Example 443

50

5

4-amino-5-(3-bromophenyl)-7-(4-piperidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine

Prepared as described for Example 440 except substituting piperidine for morpholine in step a

10

¹H NMR (300 MHz, d₆-DMSO) δ 8.61 (s, 1H), 8.57 (d, 2H), 8.02 (s, 1H), 7.88-7.90 (m, 3H), 7.80 (dt, 1H), 7.53-7.62 (m, 2H), 2.95 (m, 4H), 1.56 (m, 4H), 1.38 (m, 2H); MS (ESI) 524/526 (M⁺+H, ⁷⁹Br/⁸¹Br).

15

Example 4444-amino-5-(3-bromophenyl)-7-(4-(4-cyanopiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine

20

Prepared as described for Example 440 except substituting 4-cyanopiperidine (prepared in Ex. 436) for morpholine in step a.

25

¹H NMR (300 MHz, d₆-DMSO) δ 8.62 (s, 1H), 8.60 (d, 2H), 8.05 (s, 1H), 7.93 (s, 1H), 7.90 (m, 2H), 7.81 (dt, 1H), 7.53-7.63 (m, 2H), 3.24 (m, 2H), 2.94 (m, 1H), 2.80 (m, 2H), 1.95 (m, 2H), 1.77 (m, 2H); MS (ESI) 549/551 (M⁺+H, ⁷⁹Br/⁸¹Br).

30

Example 4454-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylmethylenesulfonamide)pyrido[2,3-d]pyrimidine

35

Prepared as described for Example 440 except substituting cyclopropylmethylamine for morpholine in step a.

40

¹H NMR (300 MHz, d₆-DMSO) δ 8.61 (s, 1H), 8.52 (d, 2H), 8.01 (d, 1H), 7.96 (d, 2H), 7.79-7.90 (m, 3H), 7.56 (m, 2H), 2.73 (m, 2H), 0.81 (m, 1H), 0.34 (m, 2H), 0.09 (m, 2H); MS (ESI) m/z 510/512 (M⁺+H, ⁷⁹Br/⁸¹Br).

45

Example 4464-amino-5-(3-bromophenyl)-7-(4-N,N-dimethylaminobenzenesulfonamide)pyrido[2,3-d]pyrimidine

50

5

Prepared as described for Example 440 except substituting dimethylamine for morpholine in step a.

10

¹H NMR (300 MHz, d₆-DMSO) δ 8.62 (s, 1H), 8.59 (d, 2H), 8.04 (s, 1H), 7.90-7.93 (m, 3H), 7.81 (dt, 1H), 7.53-7.63 (m, 2H), 2.67 (s, 6H);

5 MS (ESI) m/z 484/486 (M⁺+H, ⁷⁹Br/⁸¹Br).

15

Example 447

4-amino-5-(3-bromophenyl)-7-(4-N-(S)-2-hydroxymethylpyrrolidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine

20

10 Prepared as described for Example 440 except substituting (S-(-)-2-hydroxymethylpyrrolidine for morpholine in step a.

¹H NMR (300 MHz, d₆-DMSO) δ 8.61 (s, 1H), 8.56 (d, 2H), 8.03 (s, 1H), 7.99 (d, 2H), 7.90 (m, 1H), 7.81 (dt, 1H), 7.53-7.62 (m, 2H), 4.87 (t, 1H), 3.57 (m, 2H), 3.12 (m, 2H), 1.79 (m, 2H), 1.44 (m, 2H);

25

15 MS (ESI) m/z 540/542 (M⁺+H, ⁷⁹Br/⁸¹Br).

30

Example 448

4-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine

35

20 Prepared as described for Example 440 except substituting 4-hydroxypiperidine for morpholine in step a.

¹H NMR (d₆-DMSO) δ 8.62 (s, 1H), 8.59 (d, 2H), 8.04 (s, 1H), 7.90-7.94 (m, 3H), 7.81 (dt, 1H), 7.52-7.63 (m, 2H), 4.86 (m, 1H), 3.06 (m, 4H), 1.91 (m, 2H), 1.69 (m, 2H);

MS (ESI) m/z 540/542 (M⁺+H, ⁷⁹Br/⁸¹Br).

40

25

Example 449

4-amino-5-(3-bromophenyl)-7-(4-(cis-3,5-

dimethylmorpholinyl)benzenesulfonamide)pyrido[2,3-d]pyrimidine

45

Prepared as described for Example 440 except substituting cis-2,6-

30 dimethylmorpholine for morpholine in step a.

50

5

¹H NMR (300 MHz, d₆-DMSO) δ 8.62 (s, 1H), 8.59 (d, 2H), 8.04 (s, 1H), 7.90 (m, 3 H), 7.80 (dt, 1H), 7.52-7.61 (m, 2H), 3.53-3.66 (m, 4H), 1.89 (m, 2H), 1.05 (d, 6H); MS (ESI) m/z 554/556 (M'+H, ⁷⁹Br/⁸¹Br).

10

5

Example 4504-amino-5-(3-bromophenyl)-7-(3-fluoro-4-thiomorpholinylphenyl)pyrido[2,3-d]pyrimidine

15

Prepared as described for Example 370 using steps a and b except substituting 3-fluoro-4-thiomorpholinylacetophenone for 5-acetyl-2-chloropyridine in step a which was prepared as follows 3',4'-difluoroacetophenone and thiomorpholine are stirred in DMSO at 100° for 12 hours. The mixture is cooled and quenched with water. The resulting beige solid, 3'-fluoro-4'-thiomorpholino-acetophenone, was collected by filtration and washed with water.

20

¹H NMR (300 MHz, d₆-DMSO) δ 8.55 (s, 1H), 8.11 (m, 1H), 7.91 (s, 1H), 7.86 (m, 1H), 7.78 (dt, 1H), 7.55 (m, 2H), 7.19 (t, 1H), 3.41 (m, 4H), 2.77 (m, 4H); MS (ESI) m/z 496/498 (M'+H, ⁷⁹Br/⁸¹Br).

25

Example 4514-amino-5-(4-fluorophenyl)-7-(6-(thiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

30

Prepared as described in Example 370 except substituting thiomorpholine for 4-methoxypiperidine component and dicyanostyrene derived from 4-fluorobenzaldehyde for the 3-bromo derivative.

35

¹H NMR (300 MHz, d₆-DMSO) δ 9.06 (d, 1H), 8.52 (s, 1H), 8.44 (dd, 1H), 7.82 (s, 1H), 7.64 (m, 2H), 7.44 (m, 2H), 7.01 (d, 1H), 4.03 (m, 4H), 2.65 (m, 4H); MS (ESI) m/z 419 (M'+H).

40

Example 4524-amino-5-(4-fluorophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

50

5

Prepared by substituting Example 451 for Example 331 as described in Example 332.

10

¹H NMR (300 MHz, d₆-DMSO) δ 9.10 (d, 1H), 8.53 (s, 1H), 8.51 (dd, 1H), 7.85 (s, 1H), 7.65 (m, 2H), 7.44 (m, 2H), 7.18 (d, 1H), 4.18 (m, 4H), 3.18 (m, 4H);

5 MS (ESI) m/z 451 (M⁺+H).

15

Example 453

4-methoxy-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

Step a 4-hydroxy-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

20

Example 134 was dissolved in 10:1 acetic acid : water. The mixture was heated to reflux for 1 day and cooled. The desired product was collected by filtration.

25

The 4-hydroxy-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine was treated with K₂CO₃ (5 eq) and 18-crown-6 (7 eq) in DMF at rt. After 1 hour, methyl iodide (30 eq) added, and the reaction continued to stir at rt. After 3 hours, the reaction was quenched with water, and the resulting solid was collected by filtration and purified by chromatography to afford the title compound.

30

¹H NMR (300 MHz, d₆-DMSO) δ 9.07 (d, 1H), 8.60 (s, 1H), 8.45 (dd, 1H), 7.83 (s, 1H), 7.60 (m, 2H), 7.39 (m, 2H), 6.98 (d, 1H), 3.61-3.73 (m, 8H), 3.38 (s, 3H);

20 MS (ESI) m/z 478/480 (M⁺+H, ⁷⁹Br/⁸¹Br).

35

Example 454

4-amino-5-(3-bromophenyl)-7-(4-(4-dioxa-8-azaspiro[4.5]decan-8-ylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine

40

25 step a 4-acetylbenzoylchloride

45

4-Acetylbenzoic acid is stirred with thionyl chloride at reflux for 90 min. The solution is cooled to roomtemperature, and the thionyl chloride is removed under reduced pressure. Residual SOCl₂ is removed by evaporation with CH₂Cl₂, and the remaining yellow residue is used without further purification.

30

50

5

Step b 4-(4',4'-ethylenedioxypiperidinyl)acetophenone

10

4-acetylbenzoylchloride prepared in step a is dissolved in CH₂Cl₂ and treated with 3 eq. of 4,4-ethylenedioxypiperidine. The reaction mixture is stirred overnight at rt and is then washed with water and brine. The solution is dried (Na₂SO₄) and concentrated in vacuo to afford the desired amide.

15

Step c

20

Example 454 was prepared as described for steps a and b of Example 370, substituting the 4-(4',4'-ethylenedioxypiperidinyl)acetophenone prepared above for the 5-acetyl-2-chloropyridine in step a. Substituting the 4-(4',4'-ethylenedioxypiperidinyl)acetophenone prepared in step b for the 5 acetyl. ¹H NMR (300 MHz, d₆-DMSO) δ 8.59 (s, 1H), 8.39 (d, 2H), 7.97 (s, 1H), 7.89 (m, 1H), 7.80 (dt, 1H), 7.52-7.60 (m, 4H), 3.92 (s, 4H), 3.70 (m, 2H), 3.40 (m, 2H), 1.68 (m, 4H); MS (ESI) m/z 548/548 (M⁺+H, ⁷⁹Br/⁸¹Br).

25

15

Example 455

30

4-amino-5-(3-bromophenyl)-7-(4-(N-cyclopropylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine

35

Prepared as described for Example 454 except substituting cyclopropyl amine for 4,4-ethylenedioxypiperidine. ¹H NMR (300 MHz, d₆-DMSO) δ 8.60-8.62 (m, 2H), 8.42 (d, 2H), 7.99 (d, 1H), 7.98 (d, 1H), 7.52-7.62 (m, 2H), 2.89 (m, 1H), 0.67-0.75 (m, 2H), 0.58-0.63 (m, 2H); MS (ESI) m/z 460/462 (M⁺+H, ⁷⁹Br/⁸¹Br).

40

25

Example 456

45

4-amino-5-(3-bromophenyl)-7-(4-(morpholinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 454 except substituting morpholine for 4,4-ethylenedioxypiperidine.

50

5

¹H NMR (300 MHz, d₆-DMSO) δ 8.74 (s, 1H), 8.41 (d, 2H), 7.98 (s, 1H), 7.89 (m, 1H), 7.80 (dt, 1 H), 7.52-7.61 (m, 4H), 3.52-3.71 (m, 8H);
MS (ESI) m/z 490/492 (M⁺+H, ⁷⁹Br/⁸¹Br).

10

5

Example 4574-amino-5-(3-bromophenyl)-7-(6-N-cyclopropylamino-3-pyridyl)pyrido[2,3-d]pyrimidine

15

Prepared as described for Example 370 except substituting cyclopropyl amine for 4-hydroxypiperidine.

20

¹H NMR (300 MHz, d₆-DMSO) δ 8.99 (d, 1H), 8.52 (s, 1H), 8.40 (dd, 1H), 7.83 (m, 1H), 7.76-.780 (m, 2H), 7.51-7.58 (m, 2H), 7.40 (d, 1H), 6.73 (d, 1H), 2.62 (m, 1H), 0.76 (m, 2H), 0.48 (m, 2H);
MS (ESI) m/z 433/435 (M⁺+H, ⁷⁹Br/⁸¹Br).

25

Example 4584-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine

30

Prepared as described for Example 454 except substituting 4-hydroxypiperidine for 4,4-ethylenedioxypiperidine.

¹H NMR (300 MHz, d₆-DMSO) δ 8.59 (s, 1H), 8.40 (d, 2 H), 8.25 (s, 1H), 7.97 (s, 1H), 7.89 (t, 1H), 7.79 (dt, 1H), 7.56 (m, 3H), 5.06 (m, 1H), 3.96 (m, 2H), 3.48 (m, 2H), 1.93 (m, 2H), 1.64 (m, 2H);
MS (ESI) m/z 504/506 (M⁺+H, ⁷⁹Br/⁸¹Br).

35

Example 4594-amino-5-(3-bromophenyl)-7-(6-(S)-hydroxymethylpyrrolidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine

40

Prepared as described for Example 367 except substituting (S)-(+)2-hydroxymethylpyrrolidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane

45

50

5

¹H NMR (300 MHz, d₆-DMSO) δ 8.58 (s, 1H), 8.38 (d, 1H), 8.26 (s, 1H), 7.84 (m, 1H), 7.81 (dt, 1H), 7.57 (2 overlapping m, 2H), 7.16 (br d, 1H), 4.91 (t, 1H), 3.63 (m, 2H), 3.44 (m, 2H), 2.05 (m, 4H);
MS (ESI) m/z 478/480 (M⁺+H, ⁷⁹Br/⁸¹Br).

10

5

Example 460

15

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 4-(2-ethoxyethoxy)piperidine for 4-methoxypiperidine, which was prepared as follows. 4-Hydroxypiperidine is treated with 1 eq. of Boc₂O in CH₂Cl₂, and stirred at rt for 5 min. The solution is then washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo. The protected species is then dissolved in DMF and treated with 7 eq. of NaH. The mixture is stirred for 5 min, then 2-ethoxy-1-chloroethane (2 eq) is added, and the reaction is stirred at rt overnight. After this time, it is quenched with water and extracted with 2:1 ether-hexanes. The organic solution is dried (Na₂SO₄) and concentrated in vacuo. The oil thus obtained is finally stirred in 4M HCl-dioxane for 30 minutes. The solvent was removed in vacuo, then the residue was basified with 50% aq. NaOH solution and extracted with ether. Drying (Na₂SO₄) of the extracts, followed by removal of the solvent in vacuo, afforded the desired 4-alkoxy-piperidine.

20

¹H NMR (300 MHz, d₆-DMSO) δ 9.05 (d, 1H), 8.52 (s, 1H), 8.43 (dd, 1H), 7.85 (m, 2H), 7.78 (dt, 1H), 7.53 (m, 2H), 6.99 (d, 1H), 4.07 (m, 2H), 3.56 (m, 2H), 3.48 (m, 2H), 3.45 (q, 2H), 3.29 (m, 2H), 3.27 (m, 1H), 1.92 (m, 2H), 1.45 (m, 2H), 1.10 (t, 3H);
MS (ESI) m/z 549/551 (M⁺+H, ⁷⁹Br/⁸¹Br).

25

25

Example 461

30

4-amino-5-(3-bromophenyl)-7-(6-hexahydropyrimidine)-3-pyridyl)pyrido[2,3-d]pyrimidine

35

50

5

Prepared as described for Example 370 except substituting hexahydropyrimidine for 4-methoxypiperidine, which was prepared according to Shustov, et al Tetrahedron 1985, 41, 5719.

10

¹H NMR (300 MHz, d₆-DMSO) δ 9.23 (d, 1H), 8.89 (s, 1H), 8.58 (dd, 1H), 8.21 (s, 1H), 7.95 (m, 1H), 7.83 (m, 1H), 7.61 (m, 2H), 7.29 (d, 1H), 5.13 (m, 1H), 3.91 (m, 2H), 3.69 (m, 2H), 3.32 (m, 2H), 1.83 (m, 2H); MS (ESI) m/z 462/464 (M⁺+H, ⁷⁹Br/⁸¹Br).

15

Example 462

4-amino-5-(4,4-difluorocyclohexyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

20

Prepared as described for Example 370 except substituting 4,4-difluorocyclohexylcarboxaldehyde for 3-bromobenzaldehyde and 4,4-ethylenedioxypiperidine for 4-methoxypiperidine. The 4,4-difluorocyclohexylcarboxaldehyde was prepared as follows: 4-Oxo-cyclohexanecarboxylic acid ethyl ester was stirred with 10 eq of (diethylamino)sulfur trifluoride in benzene at rt for 24 hours. The mixture was diluted with ether and was quenched carefully with saturated NaHCO₃ solution. The organic solution was separated, washed with brine, and concentrated in vacuo to afford 4,4-difluoro-cyclohexanecarboxylic acid ethyl ester. This material was treated with 1 eq. of DIBAL-H in dry ether at -78° to afford, after workup,

25 4,4-difluoro-cyclohexanecarboxaldehyde.

30

¹H NMR (300 MHz, d₆-DMSO) δ 9.13 (d, 1H), 8.79 (s, 1H), 8.44 (dd, 1H), 8.06 (s, 1H), 7.10 (d, 1H), 3.94 (s, 4H), 3.82 (m, 4H), 1.70 (m, 4H); MS (ESI) m/z 483 (M⁺+H).

40

25

Example 463

4-amino-5-(3-bromophenyl)-7-(6-(R)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

45

Prepared as described for Example 370 except substituting (S???)₂-ethoxyethoxypyrrolidine for 4-methoxypiperidine. (R)-2-ethoxyethoxypyrrolidinyl was 30 prepared as follows:

50

5

10

15

20

25

(R)-(+)-3-Pyrrolidinol is treated with 1 eq. of Boc₂O in CH₂Cl₂ and stirred at rt for 5 min. The solution is then washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo. The protected species is then dissolved in DMF and treated with 7 eq. of NaI I. The mixture is stirred for 5 min, then 2-ethoxy-1-chloroethane (2 eq) is added, and the reaction is stirred at rt overnight. After this time, it is quenched with water and extracted with 2:1 ether-hexanes. The organic solution is dried (Na₂SO₄) and concentrated in vacuo. The oil thus obtained is finally stirred in 4M HCl-dioxane for 30 minutes. The solvent was removed in vacuo, then the residue was basified with 50% aq. NaOH solution and extracted with ether. Drying (Na₂SO₄) of the extracts, followed by removal of the solvent in vacuo, afforded the 3-alkoxy-pyrrolidine derivative.

¹H NMR (300 MHz, d₆-DMSO) δ 9.06 (d, 1H), 8.52 (s, 1H), 8.44 (dd, 1H), 7.84 (m, 2H), 7.79 (dt, 1H), 7.56 (2 overlapping m, 2H), 6.62 (br d, 1H), 4.24 (m, 1H), 3.58 (m, 4H), 3.48 (m, 4H), 3.42 (q, 2H), 2.10 (m, 2H), 1.09 (t, 3H); MS (ESI) m/z 535/537 (M⁺+H, ⁷⁹Br/⁸¹Br).

15

Example 464

30

4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-dihydroxypyridinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

35

Was prepared from Example 603 by treatment with 0.1 eq. OsO₄ and 1.2 eq. NMO in 10% MeOH-CH₂Cl₂, and the mixture was refluxed for 13 hours and was then quenched with water and filtered. The solid thus obtained was purified by recrystallization to afford the title compound.

40

¹H NMR (300 MHz, d₆-DMSO) δ 9.05 (d, 1H), 8.52 (s, 1H), 8.44 (dd, 1H), 7.85-7.77 (m, 3H), 7.58-7.5 (m, 2H), 6.58 (d, 1H), 5.0 (d, 2H), 4.17 (m, 2H), 3.6 (m, 2H).
MS m/z 480 (M⁺H)^{*}

30

Example 465

45

4-amino-5-(3-bromophenyl)-7-(6-((3aR,6aS)-2-oxo-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

50

5

Example 464 was stirred with 5 eq. of carbonyl diimidazole and 12 eq. of imidazole in DMSO at 100° for 12 hours. The solution was then cooled, quenched with water, and the resulting solid was collected by filtration and washed with water.

10

Purification by chromatography afforded the title compound.

15

5 ^1H NMR (300 MHz, d_6 -DMSO) δ 9.10 (d, 1H), 8.54 (s, 1H), 8.51 (dd, 1H), 7.87 (m, 2H), 7.78 (dt, 1H), 7.54 (m, 2H), 6.91 (d, 1H), 5.48 (m, 2H), 4.18 (d, 2H), 3.48 (m, 2H);
MS (ESI) m/z 505/507 (M^++H , $^{79}\text{Br}/^{81}\text{Br}$).

Example 466

10 4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

20

Prepared as described for Example 370 except substituting pyrroline for 4-methoxypiperidine and subsequent oxidation of this material by the following procedure: treatment with 0.1 eq. OsO_4 and 1.2 eq. NMO in 10% MeOH-CH₂Cl₂ containing a few drops of glacial acetic acid. The mixture was refluxed for 13 hours and was then quenched with water and filtered. The solid thus obtained was purified by recrystallization to afford the title compound.

25

30 ^1H NMR (300 MHz, d_6 -DMSO) δ 8.93 (s, 1H), 8.47 (s, 1H), 8.31 (d, 1H), 7.92 (t, 1H), 7.83 (dt, 1H), 7.59 (m, 2H), 7.20 (d, 1H), 4.23 (m, 2H), 3.55 (m, 4H);
20 MS (ESI) m/z 480/482 (M^++H , $^{79}\text{Br}/^{81}\text{Br}$).

35

Example 467

40 4-amino-5-(3-bromophenyl)-7-(6-(S,R-2-hydroxymethyl-4-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

45

25 Prepared as described for Example 370 except substituting (S,R)-2-hydroxymethyl-4-hydroxypyrrolidine for 4-methoxypiperidine, which was prepared as follows: N-Boc-hydroxyproline was treated with $\text{BH}_3\text{-SMc}_2$ (4 eq) in ether at roomtemperature. After 16 hours, the reaction was quenched with water and K_2CO_3 and was extracted with EtOAc. The combined extracts were dried and concentrated in vacuo to afford N-Boc-hydroxyprolinol. The Boc group was then removed (HCl-dioxane, rt).

50

5

¹H NMR (300 MHz, d₆-DMSO) δ 9.05 (d, 1H), 8.52 (s, 1H), 8.42 (dd, 1H), 7.82 (m, 2H), 7.78 (dt, 1H), 7.54 (m, 2H), 6.66 (d, 1H), 5.02 (d, 1H), 4.95 (t, 1H), 4.47 (m, 1H), 4.23 (m, 1H), 3.46-3.66 (m, 4H), 2.16 (m, 1H), 1.96 (m, 1H); MS (ESI) m/z 493/495 (M⁺+H, ⁷⁹Br/⁸¹Br).

10

5

Example 468

15 4-amino-5-(3-bromophenyl)-7-(6-(R-2-hydroxymethyl-4-pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 367 except substituting R-2-hydroxymethylpyrrolidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane
 10 ¹H NMR (300 MHz, d₆-DMSO) δ 8.58 (s, 1H), 8.38 (d, 1H), 8.26 (s, 1H), 7.84 (m, 1H), 7.80 (dt, 1H), 7.56 (2 overlapping m, 2H), 7.16 (d, 1H), 4.89 (t, 1H), 4.23 (br, 1H), 3.62 (m, 2H), 3.45 (m, 2H), 2.05 (m, 4H); MS (ESI) m/z 478/480 (M⁺+H, ⁷⁹Br/⁸¹Br).

25

15

Example 469

30 4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane for 4-methoxypiperidine, which was prepared according to

20 Portoghese, et al. J. Med. Chem. 1971, 14, 288

35 ¹H NMR (300 MHz, d₆-DMSO) δ 9.05 (d, 1H), 8.52 (s, 1H), 8.43 (dd, 1H), 7.82 (m, 2H), 7.78 (dt, 1H), 7.57 (m, 2H), 6.67 (m, 1H), 5.01 (s, 1H), 4.71 (s, 1H), 3.82 (dd, 1H), 3.68 (d, 1H), 3.54 (dd, 1H), 3.38 (d, 1H), 1.93 (m, 2H); MS (ESI) m/z 475/477 (M⁺+H, ⁷⁹Br/⁸¹Br).

40

25

Example 470

45 4-amino-5-(3-bromophenyl)-7-(6-(2-imidizolidone-1-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 1,2-ethanediamine for
 30 4-methoxypiperidine and the resulting crude product was stirred in DMSO with carbonyl

50

5

diimidazole (4.7 eq) and imidazole (9 eq) at 100° for 16 hours. Solution quenched with water, then the solvent was removed by lyophilization. Chromatography of the residue afforded the title compound.

10

IR (KBr pellet) ν_{max} 3363, 3201, 3122, 3049, 2941, 1734, 1645, 1611, 1566, 1484, 1381, 1270, 1162, 1058, 808, 781, 767 cm^{-1} ;
MS (ESI) 462/464 ($M^++\text{H}$, $^{79}\text{Br}/^{81}\text{Br}$).

15

Example 472

4-amino-5-(1,1-dimethyl-3-butenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

10 A mixture of 7.6 mmol of 2,2-dimethyl-4-pentenal (Aldrich Chemical Co.), 24.4 mmol of 1-morpholino-5-acetylpyridine, 7.6 mmol of malononitrile, and 29 mmol of ammonium acetate in ethylene dichloride was heated at 120 °C in a sealed tube for 16 hours. The reaction was cooled, poured into dichloromethane, and washed with water. The organic phase was dried over Na_2SO_4 , concentrated in vacuo, and purified by flash chromatography, eluting with ethyl acetate/dichloromethane to give the intermediate product pyridine.

20 A mixture of 1.7 mmol of this intermediate pyridine, and 45 mg of ammonium sulfate was heated in 10 mL of triethyl orthoformate at 140 °C in a sealed tube for one hour. After cooling, the reaction was poured into 40 mL of 2-M ammonia in ethanol with stirring. After 24 hours, 300 mL of hexane was added, and the solid collected by filtration to give the intermediate amidine. A mixture of 0.87 mmol of this intermediate amidine and 3 mmol of potassium t-butoxide in 10 mL of dioxane was heated at 135 °C in a sealed tube for 16 hours. After cooling, the reaction was poured into dichloromethane, washed with water, and dried over sodium sulfate. The residue was purified by flash chromatography, eluting with methanol/dichloromethane, to give the title compound as a yellow glass.

30 CHN analysis calculated for $C_{22}H_{26}N_6O$ (0.5 Methanol) C 66.48, H 6.94, N 20.67; found: C 66.18, H 6.83, N 20.65.

35 MS (FAB) calc. for $C_{22}H_{22}N_6O$: 391.2246; found: 391.2238.

40 30 IR 3417, 3340, 2965, 2853, 1603, 1584, 1563, 1533, 1241 cm^{-1} .

50

5

Example 473

10

4-amino-5-(3-bromophenyl)-7-(6-(2,4-dioxo-(1H,3H)-quinazolin-3-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

- 5 A solution of 4-aminoacetophenone and triethylamine in toluene at -78 C was
treated with phosgene, warmed to ambient temperature and concentrated under reduced
15 pressure to give 4-isocyanateacetophenone. This product was reacted with ethyl 2-
aminobenzoate in refluxing THF for 16 hours, cooled and treated with 1M potassium tert-
butoxide to give after silica gel purification 3-(4-acetylphenyl)-2,4(1H,3H)-
20 quinazolinedione. Using the procedure in Example 244c except substituting 2,4(1H,3H)-
quinazolinedione for N-methyl-5-acetylindoline gave the title compound.
MS (APCI +) m/z 537 (M+H)⁺;
¹H NMR (300 MHz, DMSO-d₆) δ 8.59 (s, 1H), 8.35 (m, 2H), 7.97 (s, 1H), 7.91 (t, 1H),
25 7.78 (m, 1H), 7.71 (dd, 1H), 7.63 (m, 1H), 7.55 (t, 1H), 7.35-7.24 (m, 3H), 6.92 (d, 1H),
15 6.72 (dt, 1H).

Example 474

30

4-amino-5-(3-bromophenyl)-7-(6-carboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine

- Prepared as described in Example 475 except substituting ammonia for
20 morpholine.
MS (APCI +) m/z 422 (M+H)⁺;
¹H NMR (300 MHz, DMSO-d₆) δ 8.87 (d, 1H), 8.66 (s, 1H), 8.62 (bs, 1H), 8.44 (d, 1H),
35 8.42 (s, 1H), 8.07 (bs, 1H), 7.88 (m, 1H), 7.83 (m, 1H), 7.63 (m, 1H), 7.58 (t, 1H).

40

25

Example 4754-amino-5-(3-bromophenyl)-7-(6-morpholinylcarboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine

45

- A solution of 3-chloro-6-pyridazinoyl chloride (Mourad et al.; J. Heterocycl. Chem., 29 6, (1992). pp1583-1592)) and triethylamine in dichloroethane was treated with
30 morpholine to give 3-chloro-6-morpholinocarboxamide pyridazine. This intermediate was

50

5

then treated with tributyl ethoxyvinyl tin under Stille conditions to give 3-acetyl-6-morpholinocarboxamide pyridazine. Treatment of this intermediate as in Example 246 replacing 3-acetyl-6-dimethylaminopyridazine gave the title compound.

10

MS (APCI +) m/z 492 (M+H)⁺;

15

5 ¹H NMR (300 MHz, DMSO-d₆) δ 8.84 (d, 1H), 8.66 (s, 1H), 8.42 (s, 1H), 8.17 (d, 1H), 7.89 (t, 1H), 7.84 (m, 1H), 7.65 (m, 1H), 7.57 (t, 1H), 3.74 (s, 4H), 3.61 (m, 2H), 3.51 (m, 2H).

Example 476

10 4-amino-5-(3-bromophenyl)-7-(6-methoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine

20

Prepared as described for Example 369 replacing benzyl alcohol with methanol.

Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the HCl salt.

25

MS (APCI +) m/z 409 (M+H)⁺;

15 ¹H NMR (300 MHz, DMSO-d₆) δ 9.90 (bs, 1H), 8.93 (s, 1H), 8.54 (d, 1H), 8.52 (s, 1H), 7.94 (t, 1H), 7.68 (m, 1H), 7.67 (m, 1H), 7.60 (d, 1H), 7.54 (d, 1H), 4.15 (s, 3H).

30

Example 477

20 4-amino-5-(3-bromophenyl)-7-(6-N,N-diethoxyethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine

35

Prepared following the procedure in Example 246 replacing dimethylamine with bis(2-ethoxyethyl)amine. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCl salt.

40

MS (APCI +) m/z 538 (M+H)⁺;

25 ¹H NMR (300 MHz, DMSO-d₆) δ 10.11 (bs, 1H), 8.89 (s, 1H), 8.40 (s, 1H), 8.26 (d, 1H), 7.89 (m, 1H), 7.81 (d, 1H), 7.64 (d, 1H), 7.58-7.46 (m, 3H), 3.88 (m, 4H), 3.63 (t, 4H), 3.44 (q, 4H), 1.09 (t, 6H).

45

Example 478

50

5

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxymethylpiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

10

4-Hydroxymethyl piperidine was treated sequentially with di-tert-butyl dicarbonate, iodoethane, and trifluoroacetic acid to give 4-ethoxymethyl piperidine which was reacted as in Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCl salt.

15

MS (APCI +) m/z 520 (M+H)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 10.08 (bs, 1H), 8.91 (s, 1H), 8.40 (s, 1H), 8.28 (d, 1H), 7.89 (s, 1H), 7.82 (d, 1H), 7.64 (d, 1H), 7.57 (t, 1H), 7.48 (bs, 1H), 4.56 (bd, 2H), 3.40 (q, 2H), 3.24 (d, 2H), 3.11 (t, 2H), 1.92 (m, 1H), 1.81 (d, 2H), 1.22 (m, 2H), 1.18 (t, 3H).

20

Example 479

25

4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranyloxy)methyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

30

4-Hydroxymethyl piperidine was treated sequentially with di-tert-butyl dicarbonate, methanesulfonyl chloride, sodium 4-tetrahydropyranoxide, and ethereal HCl to give 4-(4-tetrahydropyran)oxymethyl piperidine which was reacted as in Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the HCl salt.

35

MS (APCI +) m/z 576 (M+H)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 9.89 (bs, 1H), 8.88 (s, 1H), 8.44 (s, 1H), 8.24 (d, 1H), 7.89 (t, 1H), 7.81 (m, 1H), 7.64 (m, 1H), 7.57 (t, 1H), 7.50 (d, 1H), 7.31 (bs, 1H), 4.55 (bd, 2H), 3.78 (m, 2H), 3.52-3.22 (m, 5H), 3.07 (t, 2H), 1.89-1.79 (m, 5H), 1.41-1.16 (m, 4H).

40

25

Example 480

45

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyethoxymethyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

4-Hydroxymethyl piperidine was treated sequentially with di-tert-butyl dicarbonate, 2-chloroethyl ethyl ether and ethereal HCl to give 4-ethoxyethoxymethyl

50

5

10

15

20

25

30

35

40

45

50

piperidine which was reacted as in Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the HCl salt.

MS (APCI +) m/z 564 (M+H)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 10.13 (bs, 1H), 8.90 (s, 1H), 8.33 (s, 1H), 8.29 (d, 1H), 7.88 (s, 1H), 7.81 (d, 1H), 7.74 (d, 1H), 7.63 (d, 1H), 7.54 (t, 1H), 7.50 (s, 1H), 4.55 (bd, 2H), 3.50-3.38 (m, 6H), 3.28 (d, 2H), 3.15 (t, 2H), 1.93 (m, 1H), 1.82 (d, 2H), 1.26 (m, 2H), 1.08 (t, 3H).

10

Example 4814-amino-5-(3-bromophenyl)-7-(6-N-methyl-N-1,3-dioxolanemethylamino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane with 2-methylaminomethyl-1,3-dioxolane.

15 MS (APCI +) m/z 494 (M+H)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 8.59 (s, 1H), 8.38 (d, 1H), 8.27 (s, 1H), 7.85-7.77 (m, 2H), 7.62-7.53 (m, 2H), 7.35 (d, 1H), 5.10 (t, 1H), 3.97-3.77 (m, 6H), 3.24 (s, 3H).

Example 4824-amino-5-(3-bromophenyl)-7-(6-(1,4-dioxaspiro[4.5]decanyl-8-oxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Treatment of 1,4-dioxaspiro[4.5]decan-8-one with lithium aluminum hydride in diethyl ether provided 1,4-dioxaspiro[4.5]decan-8-ol which was subsequently treated as in Example 369 replacing benzyl alcohol to give the title compound.

25 MS (APCI +) m/z 535 (M+H)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 8.62 (s, 1H), 8.60 (d, 1H), 8.28 (s, 1H), 7.85-7.77 (m, 2H), 7.60 (m, 2H), 7.40 (d, 1H), 5.42 (m, 1H), 3.90 (s, 4H), 2.10-1.55 (m, 8H).

Example 483

50

55

5

4-amino-5-(3-bromophenyl)-7-(6-dihydroxymethylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine

10

Prepared as described for Example 369 replacing benzyl alcohol with cis 1,3-O-benzylidene glycerol. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the HCl salt.

15

MS (APCI +) m/z 469 (M+H)⁺;
¹H NMR (300 MHz, DMSO-d₆) δ 10.05 (bs, 1H), 8.93 (s, 1H), 8.51 (d, 1H), 8.50 (s, 1H), 7.92 (s, 1H), 7.82 (d, 1H), 7.66 (d, 1H), 7.59 (t, 1H), 7.53 (d, 1H), 4.59 (dd, 2H), 4.45 (dd, 2H), 3.90 (m, 1H), 3.45 (m, 2H).

20

Example 484

25

4-amino-5-(3-bromophenyl)-7-(6-(3-pyridyloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

30

Prepared as described for Example 369 replacing benzyl alcohol with 3-hydroxypyridine. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCl salt.

MS (APCI +) m/z 472 (M+H)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 10.10 (bs, 1H), 8.98 (s, 1H), 8.69 (d, 1H), 8.67 (s, 1H), 8.56 (dd, 1H), 8.51 (s, 1H), 7.93-7.79 (m, 4H), 7.68-7.53 (m, 4H).

20

Example 485

35

4-amino-5-(3-bromophenyl)-7-(6-(4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

40

Prepared as described for Example 367 replacing (1S,4S)-2-aza-5-oxabicyclo[2.2.1]heptane with 4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindole hydrochloride (SALOR) and adding potassium carbonate. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCl salt.

MS (APCI +) m/z 530 (M+H)⁺;

45

¹H NMR (300 MHz, DMSO-d₆) δ 10.03 (bs, 1H), 8.93 (s, 1H), 8.46 (s, 1H), 8.30 (d, 1H), 7.92 (m, 1H), 7.83 (dd, 1H), 7.67-7.52 (m, 3H), 7.26 (d, 1H), 4.33 (d, 1H), 3.95-3.32 (m, 4H), 2.78 (m, 1H), 2.66 (m, 1H), 1.72-1.44 (m, 4H), 1.42 (s, 3H).

50

5

Example 4864-amino-5-(3-bromophenyl)-7-(6-(4-N-ethyl-N-methoxyethyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

5 Boc-piperidine-4-carboxylic acid was coupled with N-ethylmethoxyethylamine using standard amide formation conditions to give Boc-piperidine-4-(N-ethylmethoxyethyl) carboxamide. This material was treated with HCl and the resulting amine was reacted as in Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane to give the desired product. Treatment with excess 4 M HCl in dioxane followed by
10 lyophilization gave the title compound as the di-HCl salt.
15 MS (APCI +) m/z 591 (M+H)⁺;
20 ¹H NMR (300 MHz, DMSO-d₆) δ 10.00 (bs, 1H), 8.93 (s, 1H), 8.50 (s, 1H), 8.27 (d, 1H),
25 7.92 (m, 1H), 7.83 (d, 1H), 7.67-7.45 (m, 4H), 4.59 (d, 2H), 3.55-2.95 (12H), 1.80-1.52
 (m, 4H), 1.05 (t, 3H).

15

Example 4874-amino-5-(3-bromophenyl)-7-(6-(4-N-methyl-N-methoxyethyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

The title compound was prepared following the procedure of Example 486
20 replacing N-ethylmethoxyethylamine with N-methylmethoxyethylamine.
25 MS (APCI +) m/z 577 (M+H)⁺;
30 ¹H NMR (300 MHz, DMSO-d₆) δ 10.07 (bs, 1), 8.91 (s, 1H), 8.45 (s, 1H), 8.28 (d, 1H),
35 7.90 (m, 1H), 7.82 (dd, 1H), 7.67-7.53 (m, 3H), 7.48 (bs, 1H), 4.56 (bd, 1H), 3.62-3.05 (m,
40 8H), 3.53 (s, 3H), 3.10 (s, 3H), 1.84-1.54 (m, 4H).

25

Example 4884-amino-5-(3-bromophenyl)-7-(6-(3,4-dimethoxymethoxypropylidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

50

5

Prepared as described for Example 367 replacing (1S,4S)-2-aza-5-oxa-
10 bicyclo[2.2.1]heptane with cis-3,4-bis(methoxymethoxy) pyrrolidine (Rosenberg et al.; J
Med Chem 33, 7 (1990) pp1962-1969).

10

MS (APCI +) m/z 568 (M+H)⁺;

15

⁵ ¹H NMR (300 MHz, DMSO-d₆) δ 8.58 (s, 1H), 8.40 (d, 1H), 8.26 (s, 1H), 7.85-7.76 (m,
2H), 7.62-7.50 (m, 2H), 7.12 (d, 1H), 4.72 (m, 4H), 4.37 (m, 2H), 3.80 (bm, 2H), 3.63
(bm, 2H), 3.32 (s, 6H).

Example 489

20

10 4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-
pyridazinyl)pyrido[2,3-d]pyrimidine

25

Prepared as described for Example 367 replacing (1S,4S)-2-oxa-5-
azabicyclo[2.2.1]heptane with hexahydro-1H-furo[3,4-c]pyrrole (US Patent 3910950, ICI
United States Inc. 1975). Treatment with excess 4 M HCl in dioxane followed by
lyophilization gave the title compound as the di-HCl salt.

30

15 MS (APCI +) m/z 490 (M+H)⁺;
¹H NMR (300 MHz, DMSO-d₆) δ 10.01 (bs, 1H), 8.93 (s, 1H), 8.48 (s, 1H), 8.30 (d, 1H),
7.90 (m, 1H), 7.84 (m, 1H), 7.65 (m, 1H), 7.57 (t, 1H), 7.48 (bs, 1H), 7.20 (d, 1H), 3.85
(m, 4H), 3.68-3.45 (m, 4H), 3.12 (m, 2H).

20

35

Example 490

4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-
pyridyl)pyrido[2,3-d]pyrimidine

40

Prepared as described for Example 370 replacing 4-methoxypiperidine with
25 hexahydro-1H-furo[3,4-c]pyrrole (US Patent 3910950, ICI United States Inc. 1975).
Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title
compound as the di-HCl salt.

45

MS (APCI +) m/z 489 (M+H)⁺;

50

5

¹H NMR (300 MHz, DMSO-d₆) δ 9.98 (bs, 1H), 9.03 (d, 1H), 8.88 (s, 1H), 8.67 (dd, 1H), 8.22 (s, 1H), 7.95 (m, 1H), 7.82 (dd, 1H), 7.64 (d, 1H), 7.55 (t, 1H), 7.34 (bs, 1H), 7.03 (d, 1H), 3.90-3.11 (m, 10H).

10

۵

Example 491

4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

15 pyridazinyl)pyrido[2.3-d]pyrimidine
Prepared as described for Example 367 replacing (1S,4S)-2-aza-5-oxa-
bicyclo[2.2.1]heptane with (anti)- 3-hydroxy-4-methylpyrrolidine hydrochloride (PCT
20 10 Int.Appl. (1992) WO,210191) and adding potassium carbonate. Treatment with excess 4
M HCl in dioxane followed by lyophilization gave the title compound as the di-HCl salt.
MS (APCI +) m/z 478 (M+H)⁺;
¹H NMR (300 MHz, DMSO-d₆) δ 10.06 (s, 1H), 8.93 (s, 1H), 8.42 (s, 1H), 8.35 (d, 1H),
25 7.91 (m, 1H), 7.84 (dd, 1H), 7.65 (dd, 1H), 7.57 (t, 1H), 7.50 (bs, 1H), 7.35 (d, 1H), 4.02
15 (m, 1H), 3.95-3.30 (m, 5H), 2.27 (m, 1H), 1.05 (d, 3H).

Example 492

4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

35 20 Prepared as described for Example 370 replacing 4-methoxypiperidine with (anti)-
 3-hydroxy-4-methylpyrrolidine hydrochloride (PCT Int.Appl. (1992) WO,210191) and
 potassium carbonate. Treatment with excess 4 M HCl in dioxane followed by
 lyophilization gave the title compound as the di-HCl salt.

40 25 MS (APCI +) m/z 477 ($M+H$)⁺;

¹H NMR (300 MHz, DMSO-d₆) δ 10.12 (bs, 1H), 9.00 (d, 1H), 8.90 (s, 1H), 8.78 (dd,
 1H), 8.26 (s, 1H), 7.97 (s, 1H), 7.82 (d, 1H), 7.64 (d, 1H), 7.57 (t, 1H), 7.42 (s, 1H), 7.20
 (d, 1H), 4.07-3.30 (m, 6H), 2.30 (m, 1H), 1.03 (d, 3H).

45

Example 493

50

5

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

10

Prepared as described for Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane with (anti)- 3-hydroxy-4-methylpyrrolidine hydrochloride (PCT Int.Appl. (1992) WO,210191) and potassium carbonate. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCL salt.

15 MS (APCI +) m/z 478 (M+H)⁺;

10 ¹H NMR (300 MHz, DMSO-d₆) δ 10.18 (bs, 1H), 8.92 (s, 1H), 8.42 (d, 1H), 8.26 (s, 1H), 7.91 (s, 1H), 7.83 (d, 1H), 7.70-7.51 (m, 4H), 4.40-3.64 (m, 5H), 3.30 (t, 1H), 2.38 (m, 1H), 1.18 (d, 3H).

20

Example 494

25

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

15

Prepared as described for Example 370 replacing 4-methoxypiperidine with (syn)-3-hydroxy-4-methylpyrrolidine hydrochloride (PCT Int.Appl. (1992) WO,210191) and potassium carbonate. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCL salt.

10 MS (APCI +) m/z 477 (M+H)⁺;

20 ¹H NMR (300 MHz, DMSO-d₆) δ 10.08 (bs, 1H), 8.97 (d, 1H), 8.90 (s, 1H), 8.78 (dd, 1H), 8.26 (s, 1H), 7.97 (m, 1H), 7.82 (m, 1H), 7.65 (dd, 1H), 7.57 (t, 1H), 7.42 (s, 1H), 7.20 (d, 1H), 4.26 (s, 1H), 4.10-3.22 (m, 5H), 2.38 (m, 1H), 1.08 (d, 3H).

35

Example 495

40

4-amino-5-(3-bromophenyl)-7-(6-(trans-3-cyano-4-hydroxylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

45

Prepared as described for Example 370 replacing 4-methoxypiperidine with 3-cyano-4-hydroxypyrrolidine hydrochloride (Hong et al.; J Med Chem. 40, 22, (1997) pp 3584-3593) and potassium carbonate. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCL salt.

50

5

MS (ESI +) m/z 488 (M+H)⁺;

10

¹H NMR (300 MHz, DMSO-d₆) δ 10.03 (bs, 1H), 9.08 (d, 1H), 8.88 (s, 1H), 8.65 (t, 1H), 8.20 (s, 1H), 7.95 (s, 1H), 7.82 (d, 1H), 7.62 (d, 1H), 7.55 (t, 1H), 7.32 (d, 1H), 7.00 (d, 1H), 4.65 (m, 1H), 4.15-3.50 (m, 6H).

5

Example 496

15

4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxy-4-tert-butylcarboxamidepyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

20

The compound was isolated from the reaction mixture of Example 495. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCl salt.

25

MS (ESI +) m/z 562 (M+H)⁺;
¹H NMR (300 MHz, DMSO-d₆) δ 10.03 (bs, 1H), 9.05 (d, 1H), 8.52 (s, 1H), 8.44 (dd, 1H), 7.85-7.76 (m, 3H), 7.57-7.51 (m, 3H), 7.32 (s, 1H), 6.60 (d, 1H), 5.28 (d, 1H), 4.56 (m, 1H), 3.70-3.25 (m, 4H), 3.03 (m, 1H), 1.27 (s, 9H).

30

Example 497

35

4-amino-5-(3-bromophenyl)-7-(6-(S-2-(4-tetrahydropyranyloxy)methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

40

A solution of (S)-1-Boc-2-pyrrolidinemethanol and triethylamine in dichloromethane at 0 °C was treated with methanesulfonyl chloride. The resulting mesylate was treated with 1.5 eq each of 4-hydroxytetrahydropyran and powdered potassium hydroxide in DMSO to afford the tetrahydropyranyl ether. Deprotection of the Boc amine with trifluoroacetic acid provided the free base pyrrolidine which was reacted as in Example 367 replacing (1*S*,4*S*)-2-aza-5-oxa-bicyclo[2.2.1]heptane. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCl salt.

45

MS (ESI +) m/z 562 (M+H)⁺;

50

5

¹H NMR (300 MHz, DMSO-d₆) δ 10.00 (bs, 1H), 8.93 (s, 1H), 8.49 (s, 1H), 8.30 (d, 1H), 7.91 (m, 1H), 7.84 (m, 1H), 7.64 (m, 1H), 7.58 (t, 1H), 7.49 (bs, 1H), 7.27 (bd, 1H), 4.45 (m, 1H), 3.78-3.25 (m, 9H), 2.04 (m, 4H), 1.78 (m, 2H), 1.37 (m, 2H).

10

5

Example 4984-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydropyranloxy)iminopyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

15

Equimolar amounts of 1-N-Boc-3-pyrrolidinone and O-(tetrahydro-2H-pyran-4-yl) hydroxylamine hydrochloride (JP 07173169 Takeda Chemical Industries Ltd (1995))

20

were heated at reflux in 1:1 ethanol/pyridine, cooled and concentrated to give after silica gel chromatography the desired Boc protected oxime. Deprotection with trifluoroacetic acid afforded the free base pyrrolidine which was treated as in Example 367, replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCl salt.

25

MS (ESI +) m/z 561 (M+H)⁺;

30

¹H NMR (300 MHz, DMSO-d₆) δ 10.11 (bs, 1H), 8.92 (s, 1H), 8.41 (d, 1H), 8.35 (dd, 1H), 7.90 (d, 1H), 7.83 (m, 1H), 7.65-7.33 (m, 4H), 4.38 (d, 2H), 4.25 (m, 1H), 4.10-3.72 (m, 4H), 3.44 (m, 2H), 2.93 (m, 2H), 1.93 (m, 2H), 1.55 (m, 2H).

20

Example 500

35

4-amino-5-(3-bromophenyl)-7-(5-bromo-2-thienyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 except substituting 2-acetyl-5-bromothiophene (Lancaster) for 5-acetyl-2-morpholinylthiazole.

40

MS (DCI/NH₃) m/z 463/465 (M+H)⁺;
IR (microscope) 3473, 3299, 1580, 1557, 1073 cm⁻¹.

25

Example 501

45

4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-thienyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 except substituting 3-acetyl-2,5-dimethylthiophene (Acros) for 5-acetyl-2-morpholinylthiazole.

50

5

mp: 210-212 °C;
MS (DCI/NH₃) m/z 411/413 (M+H)⁺;
IR (microscope) 3477, 3058, 1555, 1574, 1142 cm⁻¹.

10

5

Example 5024-amino-5-(3-bromophenyl)-7-(5-chloro-2-thienyl)pyrido[2,3-d]pyrimidine

15

Procedure as found in Example 357 except substituting 2-acetyl-5-chlorothiophene (Acros) for 5-acetyl-2-morpholinylthiazole.

20

mp: 264-265 °C;
MS (DCI/NH₃) m/z 417/419 (M+H)⁺;
IR (microscope) 3466, 3290, 1635, 1561, 1114 cm⁻¹.

Example 503

25

4-amino-5-(3-bromophenyl)-7-(2,4-dimethyl-5-thiazoyl)pyrido[2,3-d]pyrimidine

15 Procedure as found in Example 357 except substituting 5-acetyl-2,4-dimethylthiazole (Acros) for 5-acetyl-2-morpholinylthiazole.

30

mp: 254-255 °C; MS (DCI/NH₃) m/z 412/414 (M+H)⁺;
IR (microscope) 3477, 3299, 1648, 1563, 1285 cm⁻¹.

20

Example 504

35

4-amino-5-(3-bromophenyl)-7-(5-methyl-2-thienyl)pyrido[2,3-d]pyrimidine

40

Procedure as found in 357 except substituting 2-acetyl-5-methylthiophene (Lancaster) for 5-acetyl-2-morpholinylthiazole.
MS (DCI/NH₃) m/z 397/399 (M+H)⁺;

IR (microscope) 3294, 3218, 1618, 1581, 1065 cm⁻¹.

Example 505

45

4-amino-5-(3-bromophenyl)-7-(2-furanyl)pyrido[2,3-d]pyrimidine

Procedure as found in 357 except substituting 2-acetylfuran (Aldrich) for 5-acetyl-2-morpholinylthiazole. MS (DCI/NH₃) m/z 367/369 (M+H)⁺;

50

5

IR (microscope) 3485, 3110, 1642, 1563, 1008 cm⁻¹.

10

Example 506

4-amino-5-(3-bromophenyl)-7-(2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-5-thiazoyl)pyrido[2,3-d]pyrimidine

15

Procedure as found in 357 substituting 4,4-dioxyethylenepiperidine (Aldrich) for morpholine in Example 357a.

20

mp: >285 °C; MS (DCI/NH₃) m/z 525/527 (M+H)⁺; IR (microscope) 3493, 3087, 1648, 1584, 1142 cm⁻¹.

10

Example 507

4-amino-5-(3-bromophenyl)-7-(3-thienyl)pyrido[2,3-d]pyrimidine

25

Procedure as found in Example 357 substituting 3-acetylthiophene (Aldrich) for the product from Example 357b in 357c. MS (DCI/NH₃) m/z 383/385 (M+H)⁺; IR (microscope) 3473, 3100, 1638, 1561, 1288 cm⁻¹.

30

Example 508

4-amino-5-(3-bromophenyl)-7-(3-methyl-2-thienyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting 2-acetyl-3-methylthiophene (Lancaster) for the product from Example 357b in Example 357c. mp: 271-272 °C; MS (DCI/NH₃) m/z 397/399 (M+H)⁺; IR (microscope) 3470, 3060, 1644, 1560, 1123 cm⁻¹.

40

Example 509

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazoyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting the product from Example 509c for the product from 357b in 357c to give the title compound. mp: 278-282 °C; MS (DCI/NH₃) m/z 469/471 (M+H)⁺; IR (microscope) 3468, 3085, 1653, 1559, 1116 cm⁻¹.

45

509a: 1-Bromobutane-2,3-dione-3-oxime

50

5

2,3-butanedione (30 mL, 355 mmol; Aldrich) at 0 °C was treated with 10 drops of bromine (caution:delayed exothermic reaction). After 20 minutes, additional bromine (12.2 mL, 237 mmol) was added dropwise at such a rate as to maintain reaction temperature between 20-30 °C. Vacuum distillation (10 mmHg; fractions between 37-48 °C) provided 16.26 g (41%) of 1-bromo-2,3-butanedione compound as a yellow oil. A solution of 1-bromo-2,3-butanedione (16.26 g, 98.55 mmol) in water at 0 °C was treated dropwise with a solution of hydroxylamine hydrochloride (6.90 g, 99.29 mmol) and sodium carbonate (4.20 g, 39.63 mmol) in water (38 mL). After 1 hour, the reaction was extracted with dichloromethane, concentrated to one fourth the original volume, cooled and filtered to provide 7.08 g (40%) of the desired compound as an unstable (freezer) white solid.

10

15

20

25

30

509b: 1-(2-Morpholinothiazol-5-yl)ethanoneoxime

A solution of known morpholine-4-carbothioic acid amide (2.66 g, 18.2 mmol; J.

15 Het. Chem. 1987, 24, 1509) and the product from Example 509a (3.29 g, 18.3 mmol) in ethanol (5.5 mL) was heated to reflux for 2 hours. The reaction mixture was cooled to room temperature and the solid filtered, washed with ethanol and dried to provide 4.16 g (99%) of the desired compound as pink solid. MS (DCI/NH₃) m/z 228 (M+H)⁺.

20 509c: 1-(2-Morpholinothiazol-5-yl)ethanone

35

A solution of the product from Example 509b (6.00 g, 26.4 mmol) in water (250 mL), sulfuric acid (27 mL) and ethanol (26 mL) at 50 °C was treated dropwise with sodium nitrite (1.97 g, 28.5 mmol) as a solution in water (50 mL). After 2 hours, the mixture was cooled to 0 °C, neutralized with ammonium hydroxide and extracted with dichloromethane. The organic phases were concentrated and purified by silica gel chromatography (elution with 10% ethyl acetate/dichloromethane) to give 1.06 g (19%) the desired compound as a pink solid. MS (DCI/NH₃) m/z 213 (M+H)⁺.

40

25

45

Example 510

50

5

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-trifluoromethyl-5-thiazovl)pyrido[2,3-d]pyrimidine

10

Procedure as found in Example 357 substituting the product from Example 510a for the product from Example 357a in Example 357b to give the title compound. mp: 277-278 °C; MS (DCI/NH₃) m/z 537/539 (M+H)⁺; IR (microscope) 3481, 3061, 1607, 1544, 1116 cm⁻¹.

15

step a: 2-Morpholino-4-trifluoromethylthiazole

20

Procedure as found in Example 509b substituting 3-bromo-1,1,1-trifluoroacetone (Aldrich) for the product from Example 509a. MS (DCI/NH₃) m/z 239 (M+H)⁺.

25

Example 511

4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-thienyl)pyrido[2,3-d]pyrimidine

15 Procedure as found in 357 substituting the product from Example 511a for the product from Example 357b in Example 357c. mp: 265 °C (dec); MS (ESI) m/z 468/470 (M+H)⁺; IR (microscope) 3484, 3052, 1647, 1581, 1118 cm⁻¹.

30

511a: 5-Acetyl-2-morpholinothiophene

35

20 A solution of 5-acetyl-2-bromothiophene (8.01 g, 39.1 mmol; Aldrich) and morpholine (16 mL) was heated to 145 °C overnight. The reaction mixture was cooled and partitioned between water and dichloromethane. The organic phase was concentrated and purified by silica gel chromatography (elution with 30% hexane/ethyl acetate) to give 5.61 g (68%) of the desired compound. MS (DCI/NH₃) m/z 212 (M+H)⁺.

40

25

Example 512

4-amino-5-(3-bromophenyl)-7-(4-methyl-2-morpholinyl-5-thiazovl)pyrido[2,3-d]pyrimidine

45

Procedure as found in Example 357 substituting the product from Example 357a for the product from Example 357a in Example 357b to provide the title compound. mp:

50

5

>280 °C; MS (DCI/NH₃) m/z 483/485 (M+H)⁺; IR (microscope) 3481, 3078, 1653, 1510, 1117 cm⁻¹.

10

512a: 4-Methyl-2-morpholinothiazole

5 Procedure as in Example 509b substituting chloroacetone (Aldrich) for the product from 509a. MS (DCI/NH₃) m/z 185 (M+H)⁺.

15

10 Example 513

20 4-amino-5-(3-bromophenyl)-7-(2,5-dichloro-3-thienyl)pyrido[2,3-d]pyrimidine

25 Procedure as found in Example 357 substituting 3-acetyl-2,5-dichlorothiophene (Aldrich) for the product from Example 357b in Example 357c to provide the title compound. mp: 258-259 °C; MS (DCI/NH₃) m/z 451/453 (M+H)⁺; IR (microscope) 3477, 3060, 1651, 1564, 1044 cm⁻¹.

25

15 Example 514

30 4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-furanyl)pyrido[2,3-d]pyrimidine

35 Procedure as found in Example 357 substituting 3-acetyl-2,5-dimethylfuran (Lancaster) for the product from Example 357b in Example 357c to provide the title compound. MS (DCI/NH₃) m/z 395/397 (M+H)⁺; IR (microscope) 3492, 3092, 1641, 1581, 1222 cm⁻¹.

35

40 Example 515

45 4-amino-5-(3-bromophenyl)-7-(N-methyl-2-pyrrolyl)pyrido[2,3-d]pyrimidine

50 A solution of the product from Example 515a (3.30 g, 9.34 mmol) and triethylorthoformate (20 mL) was treated with a catalytic amount of ammonium sulfate and heated to 100 °C for 2 hours. The reaction mixture was cooled, treated with ammonia (2 M in ethanol, 50 mL) and stirred overnight. The dark mixture was then treated with sodium methoxide (3 M in methanol, 30 mL) and heated to reflux for 3 hours. The reaction was cooled, concentrated and the residue taken up in water and neutralized with 10% hydrochloric acid. The aqueous phase was extracted with dichloromethane, the

50

5

10

organic phase concentrated and purified by silica gel chromatography (elution with 5% methanol/dichloromethane) to provide 830 mg (23%) of the title compound. MS (DCI/NH₃) m/z 380/382 (M+H)⁺; IR (microscope) 3482, 3051, 1643, 1580, 1073 cm⁻¹.

15

5 S15a: 4-(3-Bromophenyl)-3-cyano-6-(2-(N-methylpyrrole)pyridine-2-amine

Procedure as found in Example 357c substituting 2-acetyl-1-methylpyrrole for the product from 357b.

MS (DCI/NH₃) m/z 353/355 (M+H)⁺.

20

10

Example 516

4-amino-5-(3-bromophenyl)-7-(2-N,N-dimethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine

25

Procedure as found in Example 357 substituting dimethylamine (40% in water, Aldrich) for morpholine in Example 357a. mp: >280 °C; MS (DCI/NH₃) m/z 427/429 (M+H)⁺; IR (microscope) 3455, 3054, 1636, 1503, 1035 cm⁻¹.

15

Example 517

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 515 substituting thiomorpholine for morpholine in Example 357a to provide the title compound. MS (DCI/NH₃) m/z 485/487 (M+H)⁺; IR (microscope) 3474, 3083, 1641, 1509, 1129 cm⁻¹.

35

Example 518

4-amino-5-(3-bromophenyl)-7-(2-(1,1-dioxidothiomorpholinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine

40

25 A solution of the product from Example 517 (402 mg, 0.83 mmol) in acetic acid and acetone was treated with potassium permanganate in water until complete consumption of starting material was detected. Reaction mixture poured over ice, the solution made strongly basic with 50% sodium hydroxide. The resulting solid was filtered and purified by silica gel chromatography (elution with 5% methanol/dichloromethane) to

50

5

provide 231 mg (54%) of the title compound as a yellow solid. MS (DCI/NH₃) m/z 517/519 (M+H)⁺; IR (microscope) 3484, 3056, 1606, 1501, 1125 cm⁻¹.

10

Example 519

5 4-amino-5-(3-bromophenyl)-7-(1-N-methyl-2-morpholinyl-5-imidazoyl)pyrido[2,3-d]pyrimidine

15

Procedure as in Example 515 substituting the product from Example 519a for the product of Example 357b in Example 357c. MS (DCI/NH₃) m/z 466/468 (M+H)⁺; IR (microscope) 3479, 3089, 1646, 1587, 1118 cm⁻¹.

20

10 519a: 4-Acetyl-1-methyl-2-morpholinylimidazole

25

A solution of 5-acetyl-2-aminooxazole (7.00 g, 55.5 mmol; J. Org. Chem. 1984, 49, 566) and morpholine (20 mL) in water (14 mL) was heated to reflux overnight. The reaction was cooled to room temperature, concentrated and triturated with ethyl acetate, filtered and dried to provide 3.52 g (33%) of the desired compound. A slurry of sodium hydride (60% in oil, 590 mg, 14.7 mmol) and methyliodide (0.86 mL, 13.7 mmol) in tetrahydrofuran (20 mL) at room temperature was added a solution of 4-acetyl-2-morpholinylimidazole (2.44 g, 12.5 mmol) in dimethylformamide (13 mL) and stirring continued for 1.5 hours. Reaction quenched with ethanol, water added and extracted with dichloromethane. The organic phases were combined, dried (Na₂SO₄), concentrated and the residue purified by silica gel chromatography (elution with 25% dichloromethane/ethyl acetate) to provide 1.27 g (49%) of the desired compound. MS (DCI/NH₃) m/z 210 (M+H)⁺.

30

35

40

25 Example 520

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-oxazoyl)pyrido[2,3-d]pyrimidine

45

Procedure as found in Example 357 substituting the product for Example 520a for the product of Example 357b in Example 357c. MS (DCI/NH₃) m/z 453/455 (M+H)⁺; IR (microscope) 3502, 3388, 1607, 1575, 1116 cm⁻¹.

30

50

5

520a: 5-Acetyl-2-morpholinooxazole

10

A solution of 2-bromo-3-oxobutyraldehyde (6.00 g, 36.4 mmol; Bull. Chem. Soc. Jpn. 1965, 38, 1158) and morpholine-4-carboxylic acid amide (9.01 g, 69.2 mmol; J. Am. Chem. Soc. 1945, 67, 1055) in acetone (40 mL) was stirred at room temperature for 1 hour then at reflux for 1 hour. The solvent removed in vacuo and the residue purified by silica gel chromatography (gradient elution with 10% ethyl acetate/dichloromethane to ethyl acetate) to provide 2.85 g (40%) of the desired compound as a yellow solid. MS (DCI/NH₃) m/z 197 (M+H)⁺.

15

10

Example 521

20

4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-methoxethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine

25

Procedure as found in Example 357 substituting the product from Example 521b for the product from Example 357b in Example 357c. MS (DCI/NH₃) m/z 471/473 (M+H)⁺; IR (microscope) 3472, 3051, 1645, 1519, 1090 cm⁻¹.

30

521a: 2-(N-methyl-N-(2-methoxyethylamino)thiazole

20

Procedure as found in Example 357a substituting (2-methoxyethyl)methylamine (TCI Japan) for morpholine. MS (DCI/NH₃) m/z 173 (M+H)⁺.

35

521b: 5-Acetyl-2-(N-methyl-N-(2-methoxyethylamino)thiazole

40

A solution of the product from Example 521a (4.98 g, 28.9 mmol) in tetrahydrofuran (150 mL) at -78 °C was treated with n-BuLi (2.3 M in hexanes, 15 mL) and stirring continued for 40 minutes. The light yellow solution was then treated with acetaldehyde (9.00 mL, 161 mmol), stirred for 15 minutes, quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate, dried (Na₂SO₄) and concentrated. The residue was taken up in dichloromethane (150 mL) and treated with manganese dioxide (5 weight equivalents) and heated to reflux for 20 hours. The reaction mixture was cooled, filtered and concentrated to provide 4.62 g (75%) of the desired compound. MS (DCI/NH₃) m/z 215 (M+H)⁺.

50

5

Example 52210 4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-ethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine

5 Procedure as found in Example 357 substituting methylethyl amine (Aldrich) for
15 (2-methoxyethyl)methylamine in Example 521a. MS (DCI/NH₃) m/z 441/443 (M+H)⁺; IR
(microscope) 3493, 3041, 1655, 1524, 1133 cm⁻¹.

Example 52320 4-amino-5-(3-bromophenyl)-7-(2-N-pyrrolidinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting pyrrolidine (Aldrich) for (2-methoxyethyl)methylamine in Example 521a. MS (DCI/NH₃) m/z 453/455 (M+H)⁺; IR (microscope) 3483, 3044, 1647, 1511, 1203 cm⁻¹.

25

15 Example 52430 4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-propylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting methylpropyl amine (Aldrich) for (2-methoxyethyl)methylamine in Example 521a to provide the title compound.

20 MS (DCI/NH₃) m/z 455/457 (M+H)⁺; IR (microscope) 3489, 3042, 1646, 1518, 1139 cm⁻¹.

35

Example 52540 4-amino-5-(3-bromophenyl)-7-(2-N,N-diethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine

Procedure as in Example 357 substituting diethylamine (Aldrich) for morpholine in Example 357a to provide the title compound. MS (DCI/NH₃) m/z 455/457 (M+H)⁺; IR (microscope) 3478, 3051, 1582, 1518, 1177 cm⁻¹.

45

Example 52650 4-amino-5-(3-bromophenyl)-7-(2-(N-methylpiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine

55

5

10

Procedure as in Example 515 substituting the product from Example 526a for the product of Example 357b in Example 357c provided the title compound. MS (DCI/NH₃) m/z 482/484 (M+H)⁺; IR (microscope) 3469, 3053, 1645, 1500, 1002 cm⁻¹.

15

5 526a: 5-Acetyl-2-(4-methylpiperazine)thiazole

20

25

30

A solution of silicon tetraisothiocyanate (2.02 g, 7.76 mmol; Can. J. Chem. 1963, 41, 2123) in toluene (30 mL) was treated with a solution of N-methylpiperazine (3.50 mL, 31.6 mmol; Acros) in toluene (10 mL) and the mixture heated to 80 °C for 20 minutes. The resulting mixture was concentrated, taken up in 10% water in isopropanol, refluxed for 20 minutes, cooled and filtered. The filtrate was concentrated and recrystallized from isopropanol to provide 3.89 g (77%) of the desired compound. A solution of the 4-methylpiperazine-1-carbothioic acid amide (3.53 g, 22.2 mmol) and 2-bromo-3-oxobutyraldehyde (3.69 g, 22.2 mmol; Bull. Chem. Soc. Jpn. 1965, 38, 1158) in acetone was refluxed for 30 minutes. The reaction mixture was cooled, quenched with saturated aqueous sodium carbonate and extracted with dichloromethane. The organic layers were combined, dried (Na₂SO₄), concentrated and the residue purified by silica gel chromatography (gradient elution with 30% acetone/dichloromethane to 5% methanol/dichloromethane) to provide 1.76 g (35%) of the desired compound as a yellow-brown solid.

20

35

Example 527

4-amino-5-(3-bromophenyl)-7-(2-(N-(2-pyridyl)piperazinyl)-5-thiazoyle)pyrido[2,3-d]pyrimidine

40

Procedure as in Example 515 substituting 1-(2-pyridyl)piperazine (Acros) for N-methylpiperazine in Example 526a. MS (ESI) m/z 545/547 (M+H)⁺; IR (microscope) 3484, 3049, 1651, 1495, 1053 cm⁻¹.

45

Example 528

4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-(2-pyridylethyl)-5-thiazoyle)pyrido[2,3-d]pyrimidine

50

5

10

Procedure as in Example 515 substituting 2-(2-(methylamino)ethyl)pyridine dihydrochloride (Acros) for N-methylpipеразине in Example 526a. MS (DCI/NH₃) m/z 518/520 (M+H)⁺; IR (microscope) 3472, 3054, 1648, 1517, 1051 cm⁻¹.

15

20

25

5

Example 5294-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine

A solution of the product from Example 506 (900 mg, 1.71 mmol) and tetrahydrofuran (12 mL) at room temperature was treated with 3 N hydrochloric acid (12 mL) and stirring continued for 24 hours. The reaction was made basic with sodium bicarbonate, extracted with dichloromethane, concentrated and the residue purified by silica gel chromatography (elution with 5% methanol/dichloromethane) to provide 263 mg (32%) of the title compound. MS (DCI/NH₃) m/z 481/483 (M+H)⁺; IR (microscope) 3482, 3084, 1716, 1508, 1074 cm⁻¹.

15

Example 5304-amino-5-(3-bromophenyl)-7-(2-(4-(N-morpholinyl)iminopiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine

30

35

A solution of Example 529 (200 mg, 0.415 mmol) and 4-aminomorpholine (Aldrich) in ethanol (5 mL) was heated to reflux for 5 hours. The solid was filtered and dried to provide 140 mg (60%) of the title compound. MS (DCI/NH₃) m/z 565/567 (M+H)⁺; IR (microscope) 3485, 3051, 1644, 1506, 1111 cm⁻¹.

40

45

Example 5314-amino-5-(3-bromophenyl)-7-(6-N-morpholine-3-pyridinesulfonamide)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting the product from Example 531b for the product from Example 357b in Example 357c. MS (DCI/NH₃) m/z 527/529 (M+H)⁺; IR (microscope) 3439, 3058, 1639, 1609, 1072 cm⁻¹.

30 531a: 5-Acetyl-2-thiopyridine

50

5

10

A solution of 5-acetyl-2-chloropyridine (10.11 g, 64.98 mmol; Tetrahedron 1992, 48, 9233) in ethanol was treated with thiourea (5.97 g, 78.4 mmol) and heated to reflux overnight. The reaction was cooled, the solid collected and taken up in 2 M sodium hydroxide. After stirring for 2 hours, the red solid was collected, acidified with glacial acetic acid. The yellow solid was collected and recrystallized from ethanol to provide 3.39 g (34%) of the desired compound.

15

MS (DCI/NH₃) m/z 154 (M+H)⁺.

531b: 5-Acetyl-2-morpholinopyridylsulfonamide

20

A suspension of the product from Example 531a (7.01 g, 45.7 mmol) in 1 M hydrochloric acid (60 mL) was treated with chlorine gas at 0 °C for 1 hour. The resulting solid was filtered, and taken up in dichloromethane (50 mL) and treated with morpholine (15 mL). After 1 hour, the mixture was quenched with 1 N hydrochloric acid and extracted with dichloromethane. The organic phases were combined, dried (Na₂SO₄) and concentrated. The residue was recrystallized from ethyl acetate to provide 6.31 g (59%) of the desired compound. MS (DCI/NH₃) m/z 271 (M+H)⁺.

30

Example 532

4-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperidinyl)-5-pyrimidyl)pyrido[2,3-d]pyrimidine
20 Procedure as found in Example 529 substituting the product from Example 533c for
35 the product from Example 506. MS (DCI/NH₃) m/z 476/478 (M+H)⁺; IR (microscope)
3469, 3051, 1644, 1561, 1108 cm⁻¹.

40

Example 533
25 4-amino-5-(3-bromophenyl)-7-(2-(4,4-dioxethylenepiperidinyl)-5-pyrimidyl)pyrido[2,3-
d]pyrimidine

45

Procedure as found in Example 515 substituting the product from Example 533b for the product from Example 357b in Example 357c and formation of the salt by treatment with HCl in diethyl ether to provide the title compound. MS (DCI/NH₃) m/z 30 520/522 (M+H)⁺; IR (microscope) 3434, 3064, 1645, 1602, 1105 cm⁻¹.

50

5

10 A solution of 5-bromo-2-chloropyrimidine (3.09 g, 16.0 mmol; J. Chem. Soc.
Chem. Commun. 1996, 2719) in ethanol (20 mL) at room temperature was treated with
5 1,4-dioxa-8-azaspiro[4.5]decane (6.00 mL, 46.8 mmol; Aldrich) and stirring continued
overnight. The reaction mixture was neutralized with saturated aqueous sodium
15 bicarbonate and extracted with dichloromethane. The organic phases were combined,
dried (Na_2SO_4), concentrated and the residue purified by silica gel column
chromatography (elution with 25% ethyl acetate/hexanes) to provide 4.78 g (99%) of the
20 desired compound as a white solid. MS (DCI/ NH_3) m/z 300/302 ($\text{M}+\text{H}$)⁺.

25 533b: 5-Acetyl-2-(1,4-dioxa-8-azaspiro[4.5]decane)pyrimidine
Procedure as found in Example 521b substituting the product from Example 533a
for Example 521a to provide the desired compound. MS (DCI/ NH_3) m/z 264 ($\text{M}+\text{H}$)⁺.
15

Example 534

30 4-amino-5-(3-bromophenyl)-7-(5-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-2-
pyrazinyl)pyrido[2,3-d]pyrimidine
Procedure as found in Example 515 substituting the product from Example 534b
20 for the product from Example 357b in Example 357c and formation of the salt by
treatment with HCl in diethyl ether to provide the title compound. MS (DCI/ NH_3) m/z
35 520/522 ($\text{M}+\text{H}$)⁺; IR (microscope) 3292, 3060, 1634, 1526, 1105 cm⁻¹.

40 534a: 5-Acetyl-2-chloropyrazine
45 A solution of 5-hydroxypyrazine-2-carboxylic acid (5.29 g, 37.76 mmol) in toluene
was treated with thionyl chloride (9.00 mL, 123 mmol) and the mixture heated to reflux
for 16 hours. The reaction mixture was concentrated and the residue taken up in
dichloromethane (200 mL) and treated with a solution of N,O-dimethylhydroxylamine
hydrochloride in 2 N sodium hydroxide. After 30 minutes, the layers were separated, the
50 organic phase dried (Na_2SO_4) and concentrated. A portion of the amide (807 mg, 4.00

55

5

mmol) was taken up in tetrahydrofuran (20 mL) cooled to -10 °C and treated with methylmagnesium bromide (3 M in diethyl ether, 4.00 mL) and warmed to room temperature. The mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic layers were dried (Na_2SO_4) and concentrated to provide 610 mg (97%) of the desired compound. ^1H NMR (CDCl_3 , 500 MHz) δ 9.00 (d, J = 1.1 Hz, 1 H), 8.63 (d, J = 1.1 Hz, 1 H), 2.70 (s, 3 H).

15

534b: 5-Acetyl-2-(1,4-dioxa-8-azaspiro[4.5]decane)pyrazine

Procedure as found in Example 511a substituting the product from Example 534a for 5-acetyl-2-bromothiophene and 1,4-dioxa-8-azaspiro[4.5]decane for morpholine. MS (DCI/ NH_3) m/z 264 ($M+\text{H}$) $^+$.

25

Example 535

4-amino-5-(3-bromophenyl)-7-(5-(4-oxopiperidinyl)-2-pyrazinyl)pyrido[2,3-d]pyrimidine

30

Procedure as found in Example 529 substituting the product from Example 534c for the product from Example 506 to provide the title compound. MS (DCI/ NH_3) m/z 476/478 ($M+\text{H}$) $^+$; IR (microscope) 3470, 3085, 1721, 1542, 1184 cm^{-1} .

35

Example 536

4-amino-5-(3-bromophenyl)-7-(6-N-cyclopropyl-3-pyridinesulfonamide)pyrido[2,3-d]pyrimidine

40

Procedure as found in Example 534c substituting cyclopropyl amine (Aldrich) for morpholine in Example 534b. MS (DCI/ NH_3) m/z 497/357 ($M+\text{H}$) $^+$; IR (microscope) 3441, 3059, 1640, 1609, 1177 cm^{-1} .

25

Example 537

4-amino-5-(3-bromophenyl)-7-(6-(N-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridylsulfonamide)pyrido[2,3-d]pyrimidine

50

5

Procedure as found in Example 534 substituting 1,4-dioxa-8-azaspiro[4,5]decane (Aldrich) for morpholine in Example 534b. MS (DCI/NH₃) m/z 583/585 (M+H)⁺; IR (microscope) 3483, 3060, 1567, 1355, 1101 cm⁻¹.

10

5

Example 538

4-amino-5-(3-bromophenyl)-7-(2-(4-(4-tetrahydropyran-4-yloxy)iminopiperidinyl)-5-pyrazinyl)pyrido[2,3-d]pyrimidine

15

Procedure as found in Example 530 substituting the product from 532 for the product from Example 529 and O-(tertahydro-2H-pyran-4-yl)hydroxylamine

20

hydrochloride (JP07173169; CAN 123:313629) for 4-aminomorpholine. MS (DCI/NH₃) m/z 575/577 (M+H)⁺; IR (microscope) 3486, 3055, 1601, 1515, 1345 cm⁻¹.

Example 539

25

4-amino-5-(3-bromophenyl)-7-(6-(4-(phenylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

30

Prepared as described for Example 359, substituting O-Benzylhydroxylamine hydrochloride for ethoxyamine hydrochloride.

MS (DCI/NH₃) m/z 580/582 (M+H; ⁷⁹Br/⁸¹Br); IR (microscope) 3486, 3297, 3060, 1603, 1579, 1557 cm⁻¹.

20

35

Example 540

4-amino-5-(3-bromophenyl)-7-(6-(4-(tert-butyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

40

Prepared as described for Example 359, substituting O-(tert-butyl)hydroxylamine hydrochloride for ethoxyamine hydrochloride.

MS (DCI/NH₃) m/z 546/548 (M+H; ⁷⁹Br/⁸¹Br); IR (microscope) 3488, 3301, 3037, 1602, 1560, 1512 cm⁻¹.

45

Example 541

50

5

4-amino-5-(3-bromophenyl)-7-(6-(4-(cyclohexyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

10 Prepared as described for Example 359, substituting O-Cyclohexylhydroxylamine hydrochloride, synthesized by the procedure of Grochowski, E; Jurczak. J. Synthesis 1976, 682 and starting with cyclohexanol, for ethoxyamine hydrochloride.
5 MS (DCI/NH₃) m/z 572/574 (M+H; ⁷⁹Br/⁸¹Br); IR (microscope) 3485, 3297, 2931, 1555,
15 1517, 1349 cm⁻¹.

Example 542

20 4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxyiminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine
25 Prepared as described for Example 359, substituting Hydroxylamine hydrochloride for ethoxyamine hydrochloride.
15 MS (DCI/NH₃) m/z 490/492 (M+H; ⁷⁹Br/⁸¹Br); IR (microscope) 3444, 3020, 2819, 1646,
15 1605, 1546 cm⁻¹.

Example 543

30 4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine
20 Prepared as described for Example 359, substituting 4-tetrahydropyranloxyamine hydrochloride, synthesized by the procedure of Grochowski, E; Jurczak. J. Synthesis
35 1976, 682 and starting with Tetrahydro-4H-pyran-4-ol, for ethoxyamine hydrochloride.
MS (DCI/NH₃) m/z 574/576 (M+H; ⁷⁹Br/⁸¹Br); IR (microscope) 3484, 3297, 3157, 2954,
15 1582, 1555 cm⁻¹.

40

25

Example 544

45 4-amino-5-(3-bromophenyl)-7-(6-(4-methoxyethoxymiminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine
30 Prepared as described for Example 359, substituting O-(2-methoxyethyl)hydroxylamine hydrochloride, synthesized by the procedure of Grochowski.

50

5

E; Jurczak. J. Synthesis 1976, 682 and starting with 2-Methoxyethanol, for ethoxyamine hydrochloride.

10

MS (DCI/NH₃) m/z 548/550 (M+H; ⁷⁹Br/⁸¹Br); IR (microscope) 3485, 3298, 3042, 1582, 1555, 1517 cm⁻¹.

5

Example 545

15

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-thienylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

20

Prepared as described for Example 359, substituting O-(2-thienylmethyl)hydroxylamine hydrochloride, synthesized by the procedure of Grochowski, E; Jurczak. J. Synthesis 1976, 682 and starting with 2-Thiophenemethanol, for ethoxyamine hydrochloride.

25

MS (DCI/NH₃) m/z 586/588 (M+H; ⁷⁹Br/⁸¹Br); IR (microscope) 3485, 3298, 3068, 1579, 1556, 1507 cm⁻¹.

15

Example 546

30

4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-(5'H-2-oxufuranyl)-4-hydroxy)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

35

Prepared as described for Example 370 except substituting 4-(4'-(5'H-2-oxyfuranyl)-4-hydroxypiperidine for 4-methoxypiperidine, which was made as follows: to a solution of 4-bromo-2-triisopropylsiloxylfuran (5.0 g, 15.7 mmol; made according to G. Jas, Synthesis 1991, 965) in THF (50 mL) at -78 °C. a solution of t-butyl lithium (1.7 M, 15 mL, 25.5 mmol) was added dropwise for 40 min. A solution of N-benzylpiperidin-4-one (4.4 mL, 23.8 mmol) was added at -78 °C. The reaction mixture was then allowed to warm up over night. Standard work-up. Column chromatographic separation (SiO₂, ethyl acetate : hexane = 1 : 2) gave 4.72 g product (70%). The product was then deprotected under H₂ in the presence of Pd(OH)₂, Et₃N in methanol.

45

MS (ESI): 559/561 (M+H; ⁷⁹Br/⁸¹Br).

IR (Mic): Vmax: 3432, 3309, 3204, 2928, 1744, 1634, 1605, 1372 cm⁻¹

30

50

5

Example 547 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(4-tetrahydropyranoyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

10

Prepared as described for Example 559 except substituting Example 548 for
5 Example 562.

15

MS (ESI): 619/621 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

IR (Mic): V_{max}: 3485, 3310, 3204, 2955, 2849, 1682, 1615, 1578, 1552, 1461, 1353, 1135, 1066 cm⁻¹.

20

10

Example 548

4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-acetyl-4'-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

25

Prepared as described for Example 367 except substituting 4-acetyl-4-hydroxypiperidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, which was prepared as
15 described in Example 562.

30

MS (ESI): 520/522 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

IR (Mic): V_{max}: 3472, 3385, 3298, 3090, 2953, 1711, 1644, 1578, 1562, 1483, 1464, 1353 cm⁻¹.

20

Example 549 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-

35

(isopropylcarboxymethoxyiminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

40

Prepared from Example 562 as described in Example 559; substituting carboxymethoxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride in
25 isopropanol as solvent

45

MS (ESI): 634/636 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

IR (Mic): V_{max}: 3450, 3311, 3174, 3068, 2984, 2937, 1737, 1674, 1647, 1606, 1555, 1440, 1373, 1201, 1136 cm⁻¹.

50

5

Example 5504-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

10

Prepared from Example 562 as described in Example 559; substituting

- 5 carboxymethoxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride in ethanol as solvent.

15

MS (ESI): 620/622 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).IR (Mic): Vmax: 3449, 3313, 3178, 3066, 2985, 1745, 1674, 1648, 1607, 1444, 1371, 1200, 1135 cm^{-1} .

20

Example 5514-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

25

Prepared from Example 562 as described in Example 559; substituting

- 15 carboxymethoxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride in methanol as solvent.

MS (ESI): 606/608 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

30

IR (Mic): Vmax: 3450, 3309, 3067, 2957, 2933, 1751, 1675, 1647, 1605, 1439, 1368, 1200, 1134 cm^{-1} .

20

35

Example 5524-amino-5-(3-bromophenyl)-7-(6-(4-(1-(2-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

40

Prepared from Example 562 as described in Example 559; substituting O-

- 25 (tetrahydro-2H-pyran-2-yl)hydroxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride.

MS (ESI): 618/620 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

45

IR (Mic): Vmax: 3449, 3306, 3197, 3066, 2949, 2872, 1675, 1648, 1607, 1442, 1370, 1200, 1135 cm^{-1} .

30

50

5

Example 553 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(allyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared from Example 562 as described in Example 559; substituting 2-propeneN-1-oxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride.

MS (ESI): 574/576 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).
IR (Mic): Vmax: 3450, 3309, 3175, 3071, 2930, 2871, 1673, 1647, 1605, 1515, 1435, 1200, 1134 cm^{-1} .

Example 554 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared from Example 562 as described in Example 559; substituting ethoxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride

MS (ESI): 562/564 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).
IR (Mic): Vmax: 3451, 3311, 3063, 2979, 2936, 2881, 1673, 1647, 1606, 1368, 1200, 1183, 1133 cm^{-1} .

Example 555 0.6)

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared from Example 562 as described in Example 559; substituting methoxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride.

MS (ESI): 548/550 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).
IR (Mic): Vmax: 3450, 3312, 3064, 2965, 2820, 1674, 1646, 1444, 1369, 1199, 1135, 1045 cm^{-1} .

Example 556 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(hydroxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared from Example 562 as described in Example 559; substituting hydroxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride.

30

50

5

MS (ESI): 534/536 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

10

IR (Mic): ν_{max} : 3448, 3313, 3198, 3070, 2881, 1782, 1676, 1650, 1610, 1448, 1371, 1200, 1137 cm^{-1} .

5

Example 557

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-tetrahydropyranloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

15

Prepared from Example 328 as described in Example 559; substituting O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride.

20

MS (ESI): 574/576 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

25

IR (Mic): ν_{max} : 3437, 3304, 3057, 2955, 2859, 2684, 1639, 1605, 1441, 1368, 1238, 1068 cm^{-1} .

15

Example 558

4-amino-5-(3-bromophenyl)-7-(6-(4-(isopropylcarboxymethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

30

Prepared from Example 328 as described in Example 559; substituting Example 328 for Example 562 and substituting carboxymethoxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride in isopropanol as solvent.

35

MS (ESI): 590/592 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

IR (Mic): ν_{max} : 3487, 3389, 3301, 3152, 3058, 2979, 2928, 2873, 1749, 1603, 1580, 1557, 1508, 1414, 1348, 1233, 1101 cm^{-1} .

40

25

Example 559

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxy-4-(1-(4-tetrahydropyranloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

45

Prepared from Example 562 as follows: to a solution of Example 562 (250 mg, 0.48 mmol) in ethanol (10 mL), 4-tetrahydropyranoxyamine hydrochloride (80 mg, 0.5 mmol; made as described from: JP 94-177353 19940729 and prepared in Example 543)

50

5

was added, followed by concentrated HCl (2 drops). The mixture was heated to reflux for about 10 hours. Standard work up, followed by chromatography (SiO₂, 5% MeOH in CH₂Cl₂) gave 156 mg (53%) of the title compound.

10

MS (ESI): 618/620 (M+H; ⁷⁹Br/⁸¹Br).

5 IR (Mic): Vmax: 3488, 3304, 3199, 2954, 2855, 1603, 1578, 1557, 1509, 1352, 1233, 1066 cm⁻¹.

15

Example 560

4-amino-5-(3-bromophenyl)-7-(6-(4-(3-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

20

Prepared as described for Example 370 except substituting 4-(4-hydroxypiperidin-4-yl)butyrolactone for 4-methoxypiperidine, which was made as follows: to a solution of 3-ethoxycarboxylpropyl triphenylphosphonium bromide (10.0 g, 22 mmol) in THF, a solution of potassium bis(trimethylsilyl)amide (0.5 M, 52 mL, 26 mmol) was added at - 78 °C. the reaction mixture was allowed to stir for 40 min at - 78 °C. N-benzyl-4-piperidinone (4.5 mL, 24 mmol) was added. The mixture stirred at -78 °C for 3 hours and then gradually warmed up to room temperature over night. Standard work up followed by chromatography (SiO₂, ethyl acetate: hexanes = 1:4) to give 5.01g product (83%). The product was then dihydroxylated as described in Example 565, and treated with p-toluenesulfonic acid in benzene to give the lactone. Debenzylation via hydrogenation gave the desired amine.

35

MS (ESI): 561/563 (M+H; ⁷⁹Br/⁸¹Br).

IR (Mic): Vmax: 3479, 3311, 3056, 2942, 2853, 2726, 1777, 1654, 1574, 1556, 1503, 1408, 1354 cm⁻¹.

40

25

Example 561

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

45

Prepared as described for Example 367 except substituting 2-(4-hydroxypiperidin-4-yl)butyrolactone for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane,

50

5

which was made from a-(1-benzyl-4-hydroxy-4-piperidyl)-*g*-butarolactone (Salor) via hydrogenation.

10

MS (ESI): 562/564 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

IR (Mic): ν_{max} : 3484, 3289, 3054, 2928, 1768, 1644, 1575, 1464, 1358, 1264, 1138 cm^{-1} .

5

Example 562

15

4-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

20

Prepared as described for Example 370 except substituting 4-acetyl-4-hydroxypiperidine for 4-methoxypiperidine, which was prepared as follows: to a solution of ethyl vinyl ether (3.8 mL, 40 mmol) in THF, a solution of t-butyllithium (1.7 M, 24 mL, 40 mmol) was added at - 78 °C. The reaction mixture was warmed up to 0 °C for about 30 min, and cooled down to - 78 °C again before transferred to a slurry of CeCl_3 (10 g, 40 mmol) in THF at - 78 °C. The mixture was stirred at -78 °C for about 1 hour, and a cold solution of N-benzyl-4-piperidinone (5.5 mL, 30 mmol) in THF was added. The reaction mixture was then gradually warmed up over night. Standard work up, followed by chromatography (SiO_2 , 1% MeOH in CH_2Cl_2) to give 7.1 g product (91%). The product was then hydrolysed to ketone product in the presence of MeOH/THF/ CH_2Cl_2 (20:30:5) mixture solvents and HCl (3N, 7 mL) at 0 °C. The product was then deprotected via hydrogenation to give the final keto-amine.

35

MS (ESI): 519/521 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

IR (Mic): ν_{max} : 3486, 3312, 3210, 2950, 2923, 2859, 1706, 1604, 1580, 1558, 1508, 1352, 1242 cm^{-1} .

40

25

Example 563

4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxyazetidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

45

Prepared as described for Example 370 except substituting 3-hydroxyazetidine for 4-methoxypiperidine, which was prepared from the N-diphenylmethyl-4-hydroxyaziridine (Maybridge) via hydrogenation.

50

5

MS (ESI): 449/451 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

IR (Mic): Vmax: 3471, 3301, 3061, 1602, 1580, 1558, 1354 cm $^{-1}$.

10

Example 564

- 5 4-amino-5-(3-bromophenyl)-7-(6-((1R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

15

Prepared as described for Example 370 except (1R,5S)-8-azabicyclo[3.2.1]octan-3-ol for 4-methoxypiperidine, which was prepared from tropanone as described by A.H. Newman, et al, J. Med. Chem. 1995, 38, 3933.

20

10 MS (ESI): 503/505 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

IR (Mic): Vmax: 3480, 3317, 3204, 2918, 1706, 1603, 1580, 1558, 1352, 1243 cm $^{-1}$.

Example 565

- 25 4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

30

15 Prepared from Example 567 as follows: to a solution of Example 567 (600 mg, 1.31 mmol) in THF/MeOH (55:5), NMO (460 mg, 3.93 mmol) was added followed by OsO₄ (35 mg, 0.14 mmol). The reaction mixture was allowed to stir over night. Quenched with sodium thiosulfate. Standard work up, followed by chromatography (SiO₂, 10% MeOH in CH₂Cl₂) to give 260 mg (40%) of the title compound.

35

20 MS (ESI): 493/495 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

IR (Mic): Vmax: 3478, 3296, 3082, 2924, 1641, 1604, 1581, 1554, 1513, 1354, 1227 cm $^{-1}$.

40

- 25 Example 566 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

45

Prepared as described for Example 367 except substituting 3-(methylaminomethyl)pyridine (Maybridge) for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane.

- 30 MS (ESI): 499/501 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

50

5

IR (Mic): Vmax: 3475, 3300, 3151, 3061, 2928, 1682, 1555, 1484, 1395, 1352 cm⁻¹.

10

Example 5674-amino-5-(3-bromophenyl)-7-(6-(1,2,3,6-tetrahydropyridyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

15

Prepared as described for Example 370 except substituting 1,2,3,6-tetrahydropyridine (Aldrich) for 4-methoxy piperidine.

MS (ESI): 459/461 (M+H; ⁷⁹Br/⁸¹Br).

IR (Mic): Vmax: 3473, 3305, 3090, 2928, 1670, 1578, 1558, 1508, 1355, 1244 cm⁻¹.

20

Example 5684-amino-5-(3-bromophenyl)-7-(6-(4-(N-4'-methoxyphenylcarbamoyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

25

Prepared as described for Example 367 except substituting 4-(N-4'-methoxyphenylcarbamoyl)piperidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, which was prepared as described in Example 570 from N-benzyl-4-hydroxypiperidine.

30

MS (ESI): 459/461 (M+H; ⁷⁹Br/⁸¹Br).

IR (Mic): Vmax: 3473, 3305, 3090, 2928, 1649, 1581, 1560, 1508, 1355 cm⁻¹.

20

Example 5694-amino-5-(3-bromophenyl)-7-(6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

40

Prepared as described for Example 370 except substituting 2-(4-hydroxypiperidin-4-yl)butyrolactone for 4-methoxypiperidine, which was made from a-(1-benzyl-4-hydroxy-4-piperidyl)-g-butarolactone (Salor) via hydrogenation.

MS (ESI): 561/563 (M+H; ⁷⁹Br/⁸¹Br).

45

IR (Mic): Vmax: 3462, 3392, 3297, 3256, 3108, 2948, 2859, 1765, 1638, 1598, 1579, 1556, 1505, 1355, 1240, 1158 cm⁻¹.

30

50

5

Example 5704-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis(N-4'-methoxyphenylcarbamoyl)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

10

Prepared as described for Example 370 except substituting 3R,4R-bis(N-4'

5

methoxyphenylcarbamoyl)pyrrolidine for 4-methoxypiperidine, which was made as follows: N-benzyl-3R,4R-dihydroxypyrrrolidine (500 mg, 2.6 mmol) (Digital) was dissolved in CH₂Cl₂ (50 mL), 4-methoxyphenylisocyanate was added at room temperature. The reaction mixture was then allowed to stir for about 8 hours. White precipitate was collected, and washed with hexanes to give a pure product (1.23 g, 96%). The benzyl

15

group was then deprotected via hydrogenation.

20

MS (ESI): 777/779 (M+H; ⁷⁹Br/⁸¹Br).

IR (Mic): Vmax: 3481, 3302, 3194, 3057, 2955, 2838, 1726, 1604, 1555, 1514, 1415, 1228, 1076, 1030, 829 cm⁻¹.

25

15

Example 5714-amino-5-(3-bromophenyl)-7-(6-((1S,5R)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

30

Prepared as described for Example 370 except substituting (1S,5R)-8-azabicyclo[3.2.1]octan-3-ol for 4-methoxypiperidine, which was made from tropane

20 (Aldrich) as described by A.H. Newman, et al. (J. Med. Chem. 1995, 38, 3933).

35

MS (ESI): 503/505 (M+H; ⁷⁹Br/⁸¹Br).

IR (Mic): Vmax: 3472, 3303, 3157, 2939, 1681, 1600, 1580, 1554, 1354 cm⁻¹.

40

25

Example 5724-amino-5-(3-bromophenyl)-7-(6-(S,S-trans-3,4-dihydroxypyrrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

45

Prepared as described for Example 370 except substituting 3S,4S-dihydroxypyrrrolidine for 4-methoxypiperidine which was prepared from the benzylprotected form (Digital) as described in Example 574.

30

MS (ESI): 479/481 (M+H; ⁷⁹Br/⁸¹Br).

50

5

IR (Mic): V_{max}: 3484, 3299, 3193, 2928, 2854, 1629, 1584, 1561, 1536, 1513, 1435, 1078 cm⁻¹.

10

Example 5735 4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

15

Prepared as described for Example 367 except substituting 3R,4R-dihydroxypyrrolidine for "(1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane" which was made as described in Example 574

10

MS (ESI): 480/482 (M+H; ⁷⁹Br/⁸¹Br).

20

IR (Mic): V_{max}: 3484, 3302, 3209, 3077, 2932, 2724, 1628, 1599, 1585, 1562, 1514, 1433 cm⁻¹.

25

Example 57415 4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

30

Prepared as described for Example 370 except substituting 3R,4R-dihydroxypyrrolidine for 4-methoxypiperidine and was prepared as follows: To a solution of N- benzyl-3R,4R-dihydroxypyrrolidine (Digital; 1.4 g, 7.25 mmol) in methanol,

20 Pd(OH)₂ on carbon (300 mg) was added followed by H₂ (1 atom.) at room temperature over night. Standard work up gave 635 mg of the product (85%).

35

MS (ESI): 479/481 (M+H; ⁷⁹Br/⁸¹Br).IR (Mic): V_{max}: 3484, 3303, 3208, 2932, 2861, 1585, 1562, 1538, 1513, 1434, 1078 cm⁻¹.

40

25

Example 57545 4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

30 Prepared as described for Example 370 except 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (Acros) for 4-methoxypiperidine.

50

5

MS (ESI): 607/609 ($M+H$; $^{79}Br/^{81}Br$).

IR (Mic): ν_{max} : 3427, 3321, 3055, 1776, 1644, 1607, 1533, 1445, 1373, 1246 cm^{-1} .

10

Example 576

5 4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-oxo-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

15

Prepared from Example 586 as follows: to a solution of Example 586 (250 mg, 0.47 mmol) in CH_2Cl_2 at 0 °C, mCPBA was added in small portion. The reaction was monitored by TLC. After reaction completion, quenched with sodium thiosulfate.

20

10 Standard work-up, followed by chromatography purification (SiO_2 , 10% MeOH in CH_2Cl_2) to give 152 mg of the title compound (59%).

MS (ESI): 551/553 ($M+H$; $^{79}Br/^{81}Br$).

25

IR (Mic): ν_{max} : 3474, 3384, 3305, 3062, 2918, 1603, 1581, 1561, 1511, 1413, 1352, 1228 cm^{-1} .

15

Example 577

30 4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4,4-dioxido-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

30

Prepared from Example 586 as follows: to a solution of Example 586 (300 mg, 0.56 mmol) in acetic acid at 0 °C, a solution of $KMnO_4$ in water was added till the color stayed. Quenched with sodium thiosulfate. Standard work up, followed by chromatography separation (SiO_2 , 5% MeOH in CH_2Cl_2) to give 151 mg of the title compound (48%).

MS (ESI): 567/569 ($M+H$; $^{79}Br/^{81}Br$).

40

IR (Mic): ν_{max} : 3475, 3348, 3210, 3061, 2955, 1694, 1585, 1308, 1235 cm^{-1} .

25

Example 578

45 4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-4-one for 4-methoxypiperidine as follows: 1-phenyl-1,3,8-

50

5

10

15

20

25

30

40

50

triazaspiro[4.5]decaN-4-one (Acros; 350 mg, 1.5 mmol) was used to react with the chloride intermediate (200 mg, 0.48 mmol) in DMSO at 100 °C for over night. There were two major products, one of them was the desired compound (95 mg, 33%).

MS (ESI): 605/607 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

IR (Mic): Vmax: 3486, 3325, 3194, 3056, 2957, 2870, 1719, 1602, 1580, 1559, 1533, 1353, 1256 cm⁻¹.

Example 579

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazoliny)l)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 367 except substituting 4-(2-keto-1-benzimidazoliny)l)piperidine (Aldrich) for "(1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane".

MS (ESI): 594/596 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

IR (Mic): Vmax: 3435, 3347, 3063, 1690, 1631, 1610, 1554, 1484, 1375 cm⁻¹.

15

Example 580

4-amino-5-(3-bromophenyl)-7-(6-(4-oxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared from Ex. 328 as follows: to a solution of Example 328 (400 mg, 0.84 mmol) in acetic acid, H₂O₂ (30%) was added till all the starting material was converted to the desired product. Standard work up, followed by chromatography (SiO₂, 10% MeOH in CH₂Cl₂) gave 301 mg of the title compound (72%).

MS (ESI): 495/497 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

IR (Mic): Vmax: 3440, 3060, 2869, 1695, 1645, 1606, 1484, 1372, 1243 cm⁻¹.

MS (ESI): 495/497 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

Example 581

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazoliny)l)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

55

5

Prepared as described for Example 370 except substituting 4-(2-keto-1-benzimidazolinyl)piperidine (Aldrich) for 4-methoxypiperidine.

10

MS (ESI): 593/595 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

15

IR (Mic): Vmax: 3473, 3304, 3063, 2918, 1603, 1581, 1512, 1413, 1353, 1228 cm^{-1} .

5

Example 582

15

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(2-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine

20

Prepared as described for Example 370 except substituting 2-(2'-methylaminoethyl)pyridine (Aldrich) for 4-methoxypiperidine.

25

MS (ESI): 512/514 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

30

IR (Mic): Vmax: 3475, 3303, 3046, 2931, 1648, 1583, 1561, 1519, 1405, 1354, 1142 cm^{-1} .

25

15

Example 583

30

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(4-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine

35

Prepared as described for Example 370 except substituting 4-(2'methylaminoethyl)pyridine (Aldrich) for 4-methoxypiperidine.

MS (ESI): 512/514 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

40

IR (Mic): Vmax: 3480, 3252, 3000, 1600, 1590, 1570, 1350 cm^{-1} .

Example 584

45

4-amino-5-(3-bromophenyl)-7-(6-N-(3-pyridylmethyl)amino-3-pyridyl)pyrido[2,3-d]pyrimidine

50

Prepared as described for Example 370 except substituting 3-(aminomethyl)pyridine (Aldrich) for 4-methoxypiperidine.

MS (ESI): 484/486 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

IR (Mic): Vmax: 3477, 3289, 3233, 3040, 1640, 1610, 1558, 1480, 1392, 1353, 1310, 1145 cm^{-1} .

5

Example 5854-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

10 5 Prepared as described for Example 370 except substituting 2-(hydroxymethyl)piperidine (Aldrich) for 4-methoxypiperidine.

15 15 MS (ESI): 491/493 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

IR (Mic): Vmax: 3479, 3396, 3299, 3076, 2935, 2858, 1643, 1600, 1580, 1558, 1506, 1418, 1351 cm^{-1} .

10 20

Example 5864-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

25 25 Prepared from Ex. 328 as follows: to a slurry of Example 328 (1.0 g, 2.1 mmol) in

15 15 CH_2Cl_2 (220 mL), thioethanol (295 mL, 4.2 mmol) was added followed by BF_3 etherate (535 mL, 4.2 mmol). The mixture stirred at room temperature for 1 day, and quenched with NaHCO_3 (sat.). Standard work up, the crude product mixture was then recrystallized from $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{hexanes}$ to give the title compound (902 mg, 80%).

30 30 MS (ESI): 535/537 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

20 20 IR (Mic): Vmax: 3487, 3471, 3291, 3048, 2949, 2858, 1642, 1603, 1560, 1511, 1418, 1353, 1227, 1085 cm^{-1} .

35

Example 5874-amino-5-(3-bromophenyl)-7-(6-(4-hydroxy-4-(4-bromophenyl)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

40

25 25 Prepared as described for Example 370 except substituting 4-(4'-bromophenyl)-4-hydroxypiperidine (Aldrich) for 4-methoxypiperidine.

45 45 MS (ESI): 633/635 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

IR (Mic): Vmax: 3483, 3296, 3055, 2944, 1645, 1604, 1561, 1531, 1506, 1430, 1340, 1238 cm^{-1} .

50

5

Example 5884-amino-5-(3-bromophenyl)-7-(6-(4-N-(2-pyridnyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

10 Prepared as described for Example 370 except substituting 1-(2'-pyridino)piperazine (Aldrich) for 4-methoxypiperidine.
15 MS (ESI): 539/541 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).
 IR (Mic): Vmax: 3476, 3289, 3052, 2929, 2843, 1642, 1597, 1559, 1481, 1398, 1231 cm⁻¹.

20
20Example 589

25 Prepared as described for Example 370 except substituting 1-(2-(2-hydroxyethoxy)ethyl)piperazine (Aldrich) for 4-methoxypiperidine..
30 MS (ESI): 550/552 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).
 IR (Mic): Vmax: 3490, 3396, 3279, 3143, 2919, 2852, 1633, 1604, 1582, 1555, 1504, 1424, 1337, 1241, 1119 cm⁻¹.

20

Example 590

35 4-amino-5-(3-bromophenyl)-7-(6-(4,4-diacetoxyethylthio)piperidiny)-3-pyridyl)pyrido[2,3-d]pyrimidine
40 Prepared as described for Example 370 except substituting 4,4-di(2'-acetoxyethaN-1-thio)piperidine for 4-methoxypiperidine. This amine was prepared was made as follows:
45 to a solution of 4-piperidinone hydrochloride salt (5.0 g, 32.6 mmol) in acetic acid (100 mL), 2-thioethaN-1-ol (3 mL, 42.8 mmol) was added followed by BF₃ etherate (9.0 mL, 71.0 mmol) at room temperature. The reaction mixture was allowed to stir at room temperature for 3 days, and standard work-up gave a crude product 8.28 g (86%).
 MS (ESI): 697/699 (M+H; $^{79}\text{Br}/^{81}\text{Br}$).

50

5

IR (Mic): Vmax 3482, 3300, 3058, 2944, 2853, 1738, 1602, 1574, 1560, 1508, 1352, 1231 cm⁻¹.

10

Example 5915 4-amino-5-(3-bromophenyl)-7-(6-(N-methy-N-(3-pyridylmethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine

15

Prepared as described for Example 370 except substituting 3-(methylaminomethyl)pyridine (Maybridge) for 4-methoxypiperidine.

MS (ESI): 498/500 (M+H; ⁷⁹Br/⁸¹Br).

20

10 IR (Mic): Vmax: 3477, 3298, 3092, 2923, 1645, 1604, 1559, 1516, 1399, 1356 cm⁻¹.

Example 59225 4-amino-5-(3-bromophenyl)-7-(6-(4-pyrrolidinylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

15 Prepared as described for Example 370 except substituting 4-(1-pyrrolidinyl)piperidine (Aldrich) for 4-methoxypiperidine

MS (ESI): 554/556 (M+H; ⁷⁹Br/⁸¹Br).

30

IR (Mic): Vmax: 3474, 3299, 3042, 2807, 1647, 1601, 1574, 1560, 1507, 1231 cm⁻¹.

20 Example 593 4-amino-5-(3-bromophenyl)-7-(6-(2-(1H-imidazol-4-yl)ethylamino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

35

4-Amino-5-(3-bromophenyl)-7-(6-chloropyridaz-3-yl)pyrido[2,3-d]pyrimidine (165mg), prepared in Example 367, histamine (133mg), and potassium carbonate (166mg) were suspended in pyridine (2ml) and heated at 110°C for 20h. The reaction mixture was then directly chromatographed (TFA/MeOH/CH₂Cl₂) to give the title compound.

40

mp: δ 235°C; MS (ESI)* m/z: 488/490.

IR (cm⁻¹): 3475, 3301, 3199, 1721, 1625, 1580, 1553, 1467, 1357, 1133.

45

Example 594

50

5

4-amino-5-(3-bromophenyl)-7-(6-(4-N-cyanomethylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

10

Prepared by deformylation of Example 329 with hydrochloric acid in methanol and followed by treatment with iodoacetyl nitrile in dimethylformamide.

- 5 IR (mic) 3473, 3299, 2822, 1561, 1234 cm⁻¹;
MS m/z 502 (M+H)⁺.

15

Example 595

20

4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxypyrroldinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

25

Prepared as described for Example 370 except substituting 3-hydroxypyrrolidine for 4-methoxypiperidine.

25

- IR (microscope) 3480, 3300, 1606, 1559, 1431, 1309 cm⁻¹;
MS m/z 463 (M+H)⁺.

15

Example 596

30

4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

35

Prepared as described for Example 370 except substituting 3-methylpiperidine for 4-methoxypiperidine.

35

- IR (microscope) 3473, 3092, 1558, 1506, 1233 cm⁻¹;
MS m/z 476 (M+H)⁺.

40

Example 597

4-amino-5-(3-bromophenyl)-7-(6-(cis-3,5-dimethylmorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

45

Prepared as described for Example 370 except substituting cis-3,5-dimethylmorpholine for 4-methoxypiperidine.

IR (microscope) 3475, 3090, 1561, 1508, 1239, 1175 cm⁻¹

30 MS m/z 492 (M+H)⁺.

50

5

Example 598

4-amino-5-(3-bromophenyl)-7-(6-(4,4-difluoropipridinyl)-3-pyridyl)pyrido[2,3-
d]pyrimidine

5 Prepared as described for Example 370 except substituting 4,4-difluoropiperidine
for 4-methoxypiperidine, 4,4-difluoropiperidine was prepared according to Tetrahedron,
1977, 33, 1707

IR (microscope) 3474, 3091, 1507, 1237 cm^{-1} ; MS m/z 498 ($M+H^+$).

Example 599

Example 599

4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidovthiomorpholinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared by the oxidation of Example 605 using OsO₄ in MeOH/CH₂Cl₂/acetone (1:1:1) solution.

15 IR(KBr) 3470, 1600, 1564, 1316, 1287, 1122 cm⁻¹
MS m/z 513 (M+H)⁺.

30 Example 600

Example 600

4-amino-5-(3-bromophenyl)-7-(6-thiazolidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

20 Prepared according to the procedure of Example 306.

IR (microscope) 3468, 3052, 1557, 1509, 1407, 1289 cm^{-1} ; MS m/z 466 ($M+\text{H}$)⁺.

Example 601

4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidothiazolidin-3-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared according to the procedure of Example 306.

IR (microscope) 3466, 3090, 1563, 1508, 1234 cm^{-1} ; MS m/z 498 ($M+H$)⁺.

45

Example 602

30 4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine

50

5

Prepared as described for Example 367 except substituting thiomorpholine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane.

10

IR (microscope) 3426, 3063, 1605, 1556, 1442, 1377, 1265 cm⁻¹; MS m/z 481 (M+H)⁺.

5

Example 603

4-amino-5-(3-bromophenyl)-7-(6-(2,5-dihdropyrrolyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

15

Prepared according to the procedure of Example 306.

IR (microscope) 3468, 3060, 1607, 1550, 1443, 1265 cm⁻¹; MS m/z 446 (M+H)⁺.

20

10

Example 604

4-amino-5-(3-bromophenyl)-7-(6-(1,3-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

25

Prepared according to the procedure in Example 346, with potassium-t-butoxide and dibromomethane in dimethylformamide.

15

IR (microscope) 3468, 3052, 1557, 1509, 1407, 1289 cm⁻¹; MS m/z 520 (M+H)⁺.

30

Example 605

4-amino-5-(3-bromophenyl)-7-(6-hydroxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared according to the procedure of Example 246c substituting thiomorpholine for dimethylamine.

35

IR(KBr) 3487, 1601, 1562, 1502, 1128 cm⁻¹

MS m/z 481 (M+H)⁺

40

25

Example 606

4-amino-5-(2,3-dichlorophenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

45

The procedure of Example 392 was followed, except substituting 5-acetyl-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)pyridine for 5-acetyl-2-morpholinylpyridine. Treatment with HCl/ethanol to form the hydrochloride salt was omitted, and the free base was obtained instead.

50

5

IR (MIC) 3480, 3120, 1635, 1605, 1561, 1515, 1429, 1240cm⁻¹; MS m/z 507 (M-H)⁺

10

Example 607

4-amino-5-isopropyl-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

15

Prepared by the method of Example 327, substituting 2-methylpropanal for 3-bromobenzaldehyde.

20

mp: ~ 205°C;
MS (FAB)⁺ m/z calc'd for C₂₂H₂₁N₆O₂: 407.2195, found: 407.2186.
IR (cm⁻¹): 3318, 3142, 2960, 1586, 1554, 1514, 1425, 1344, 1240, 1105.

Example 608 .3

4-amino-5-(3-bromophenyl)-7-(6-piperidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

25

The title compound was prepared as described for Example 370 substituting

15 piperidine for 4-methoxypiperidine, followed by treatment with 1M HCl ether
MS (APCI+) m/z 461 (M+H)⁺;
¹H NMR (300 MHz, DMSO-d₆) δ 10.05 (bs, 1H), 9.00 (m, 1H), 8.90 (s, 1H), 8.70 (m, 1H),
30 8.23 (m, 1H), 7.82 (m, 1H), 7.60 (m, 2H), 7.40 (m, 2H), 3.87 (m, 4H), 1.68 (m, 6H)

20

Example 609

35

4-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydropyranoyloximino)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

40

The title compound was prepared as described for Example 370 substituting 3-(4'-tetrahydropyranyl-oximino)pyrrolidine (prepared as in A-321236.3) for 4-methoxypiperidine, followed by treatment with 1M HCl ether.

45

MS (ESI+) m/z 560 (M+H)⁺;
¹H NMR (300 MHz, DMSO-d₆) δ 10.00 (bs, 1H), 9.14 (s, 1H), 8.90 (s, 1H), 8.65 (m, 1H),
7.97 (s, 1H), 7.82 (m, 1H), 7.60 (m, 2H), 7.38 (m, 1H), 7.04 (m, 1H) 4.39 (m, 2H), 4.25
(m, 1H), 3.84 (m, 4H), 3.42 (m, 2H), 2.94 (m, 2H), 1.94 (m, 2H), 1.57 (m, 2H)

50

5

Example 610 4-amino-5-(2-trifluorophenylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

10

Prepared as described for Example 395 except substituting 2-trifluoromethylbenzaldehyde for 2,5-dichlorobenzaldehyde.

5 IR (KBr) 3495, 1674, 1634, 1487, 1421, 1321, 1302, 1190cm⁻¹;
MS m/z 452.9 (M+H)⁺.

15

20

25

30

35

40

45

50

55

Claims

5

10

15

20

25

30

35

40

45

50

55

5

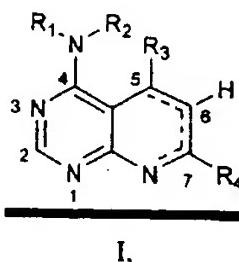
WHAT IS CLAIMED IS:

10

1. A method of inhibiting adenosine kinase by administering to a mammal in need of such treatment a pharmaceutically effective amount of one or more compounds of formula I

15

5



I,

20

or a pharmaceutically acceptable salt or amide thereof in vitro or to a mammal wherein,

25

R¹ and R² are each independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl, heterocycle, heterocyclealkyl, heterocyclecarbonyl, hydroxyalkyl, iminoalkyl, and (NZ₁Z₂)alkyl, or R¹ and R² may join together with the nitrogen atom to which they are attached to form a 5-7 membered ring optionally containing 1-2 additional heteroatoms selected from the group consisting of O, N, and S;

35

Z₁ and Z₂ are each independently selected from the group consisting of hydrogen, alkoxy carbonyl, alkyl, alkylcarbonyl, benzyl, benzyloxycarbonyl, and formyl;

40

R³ is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, (NZ₁Z₂)alkyl, and -R^AR^B;

R^A is selected from the group consisting aryl and arylalkyl;

45

R^B is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

50

R⁴ is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and -R^CR^DR^E;

5

R^C is selected from the group consisting of aryl, arylalkyl, heterocycle, and heterocyclealkyl;

10

R^D is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycloxyalkyl, heterocycloxyimino, heterocycloxyiminoalkyl, and heterocyclesulfonyl;

15

R^E is absent or selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycloxyalkyl, heterocycloxyimino, heterocycloxyiminoalkyl, and heterocyclesulfonyl; and a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;

20

with the proviso that the following compounds are excluded,

25

4-amino-5-(4-chlorophenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine,

15 4-amino-5-(4-methoxyphenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(4-fluorophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(4-chlorophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-phenyl-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-phenyl-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,

20 4-amino-5-(4-methoxyphenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine,

35

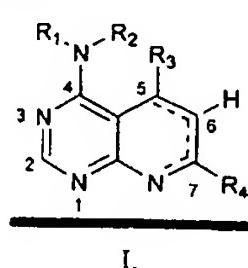
4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine, and

4-amino-5,7-diphenylpyrido[2,3-d]pyrimidine.

40

2. A method of inhibiting adenosine kinase according to claim 1 comprising
25 administering a compound of formula I

45



50

5

or a pharmaceutically acceptable salt or amide thereof wherein,

R¹ and R² are each independently selected from the group consisting of hydrogen,

10 alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl,

5 heterocyclealkyl, hydroxyalkyl, iminoalkyl, and (NZ₁Z₂)alkyl, or R¹ and R² may join together with the nitrogen atom to which they are attached to form a 6 membered ring 15 optionally containing 1 additional heteroatom selected from the group consisting of O, N, and S;

R³ is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl,

20 cycloalkyl, heterocycle, heterocyclealkyl, (NZ₁Z₂)alkyl, and -R^AR^B;

R^A is selected from the group consisting of aryl and arylalkyl;

25 R^B is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, and heterocycle;

R⁴ is selected from the group consisting of alkoxyalkynyl, alkynyl, aryl,

15 heterocycle, and -R^CR^DR^E;

R^C is selected from the group consisting of aryl and heterocycle;

30 R^D is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleoxy, and heterocyclesulfonyl;

20 R^E is absent or selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocleoxyalkyl, heterocleoxyimino, and heterocleoxyiminoalkyl;

35 Z₁ and Z₂ are each independently selected from the group consisting of hydrogen,

40 alkoxycarbonyl, alkyl, alkylcarbonyl, benzyl, benzyloxycarbonyl, and formyl; and

45 a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained.

45
3. A method of inhibiting adenosine kinase according to claim 1 comprising
30 administering a compound of formula II

50

55

5

10

15

20

25

30

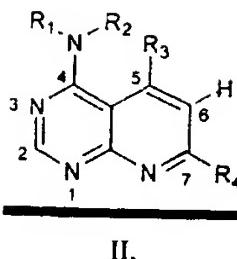
35

40

45

50

55



or a pharmaceutically acceptable salt or amide thereof wherein,

R^1 and R^2 are each independently selected from the group consisting of hydrogen,

5 alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl, heterocyclealkyl, hydroxyalkyl, iminoalkyl, and $(NZ_1Z_2)alkyl$, or R^1 and R^2 may join together with the nitrogen atom to which they are attached to form a 6 membered ring optionally containing 1 additional heteroatom selected from the group consisting of O, N, and S;

R^3 is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heterocyclealkyl, $(NZ_1Z_2)alkyl$, and $-R^A R^B$;

R^A is selected from the group consisting of aryl and arylalkyl;

R^B is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, and heterocycle;

R^4 is selected from the group consisting of alkoxyalkynyl, alkynyl, aryl, heterocycle, and $-R^C R^D R^E$;

R^C is selected from the group consisting of aryl and heterocycle;

R^D is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleoxy, and heterocyclesulfonyl;

R^E is absent or selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, and heterocycleoxyiminoalkyl; and,

Z_1 and Z_2 are each independently selected from the group consisting of hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, benzyl, benzyloxycarbonyl, and formyl.

5

4. The method according to claim 3 wherein R⁴ is selected from the group consisting of:
- 10 phenyl; thiophene-2-yl; 3-methyl-2-oxobenzoxazolin-6-yl; 2-(dimethylamino)-5-pyrimidinyl; 2-(N-formyl-N-methyl amino)-5-pyrimidinyl; 2-(N-methoxyethyl-N-methyl amino)-5-pyrimidinyl; 2-(N-methylamino)5-pyrimidinyl; 2-(1-morpholinyl)-5-pyrimidinyl; 2-(1-pyrrolidinyl)-5-pyrimidinyl; 2-dimethylamino-5-pyrimidinyl; 2-furanyl; 2-oxobenzoxazolin-6-yl; 2-pyridyl; 3-(dimethylamino)phenyl; 3-amino-4-methoxyphenyl; 3-bromo-4-(dimethylamino)phenyl; 3-methoxyphenyl; 3-methyl-4-(N-acetyl-N-methylamino)phenyl; 3-methyl-4-(N-formyl-N-methylamino)phenyl; 3-methyl-4-(N-methylamino)phenyl; 3-methyl-4-pyrrolidinylphenyl; 3-pyridyl; 3,4-dichlorophenyl; 3,4-methylenedioxypyhenyl; 3,4,5-trimethoxyphenyl; 4-(acetylamino)phenyl; 4-(dimethylamino)-3-fluorophenyl; 4-(dimethylamino)phenyl; 4-(imidazol-1-yl)phenyl; 4-(methylthio)phenyl; 4-(morpholinyl)phenyl; 4-(N-(2-(dimethylamino)ethyl)amino)phenyl; 4-(N-(2-methoxyethyl)amino)phenyl; 4-(N-acetyl-N-methylamino)phenyl; 4-(N-ethyl-N-formylamino)phenyl; 4-(N-ethylamino)phenyl; 4-(N-formyl-N-(2-methoxyethyl)amino)phenyl; 4-(N-isopropylamino)phenyl; 4-(N-methyl-N-(2-dimethylamino)ethyl)amino)phenyl; 4-(N-methyl-N-(2-(N-phthalimidyl)acetyl)amino)phenyl; 4-(N-methyl-N-(2-cyano)ethylamino)phenyl; 4-(N-methyl-N-(2-methoxyethyl)amino)phenyl; 4-(N-methyl-N-(3-methoxy)propionylamino)phenyl; 4-(N-methyl-N-acetylamino)phenyl; 4-(N-methyl-N-formylamino)phenyl; 4-(N-methyl-N-trifluoroacetylamino)phenyl; 4-(N-morpholinyl)phenyl; 4-(thiophene-2-yl)phenyl; 4-(ureido)phenyl; 4-(2-dimethylamino)acetylamino)phenyl; 4-(2-methoxy)acetylamino)ethyl)amino)phenyl; 4-(2-methoxy)ethoxyphenyl; 4-(2-oxo-3-oxazolidinyl)phenyl; 4-(4-methoxy-2-butyl)phenyl; 4-(4-methylpiperidinyl)phenyl; 4-(5-pyrimidinyl)phenyl; 4-aminophenyl; 4-bromophenyl; 4-butoxyphenyl; 4-carboxamidophenyl; 4-chlorophenyl; 4-cyanophenyl; 4-diethylaminophenyl; 4-diethylmalonylallylphenyl; 4-dimethylaminophenyl; 4-ethoxyphenyl; 4-ethylphenyl; 4-fluorophenyl; 4-hydroxyphenyl; 4-imidazolylphenyl; 4-

50

55

5

- iodophenyl; 4-isopropylphenyl; 4-methoxyphenyl; 4-methylaminophenyl; 4-methylsulfonylphenyl; 4-morpholinylphenyl; 4-N-(2-(dimethylamino)ethyl)-N-formylamino)phenyl; 4-N-(3-methoxypropionyl)-N-isopropyl-amino)phenyl; 4-N-ethyl-N-(2-methoxyethyl)amino)phenyl; 4-N-formylpiperazinylphenyl) 4-nitrophenyl; 4-piperidinylphenyl; 4-(3-pyridyl)phenyl; 4-pyrrolidinylphenyl; 4-t-butylacrylphenyl; 5-(dimethylamino)thiophene-2-yl; 5-amino-2-pyridyl; 5-dimethylamino-2-pyrazinyl; 3-dimethylaminopyridazin-6-yl; 5-dimethylamino-2-pyridyl; 5-pyrimidinylphenyl; 6-(N-methyl-N-formylamino)-3-pyridinyl; 6-(N-methyl-N-methoxyethylamino)-3-pyridinyl; 6-(2-oxo-3-oxazolidinyl)-3-pyridinyl; 6-dimethylamino-3-pyridinyl; 6-imidazolyl-3-pyridinyl; 6-morpholinyl-3-pyridinyl; 6-pyrrolidinyl-3-pyridinyl; 6-(2-propyl)-3-pyridinyl; (4-formylamino)phenyl; 6-(4-oxopiperidinyl)-3-pyridazinyl; 6-(4-morpholinyliminopiperidinyl)-3-pyridazinyl; 6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridazinyl; 6-(4-methoxyiminopiperidinyl)-3-pyridazinyl; 6-phenylmethoxy-3-pyridazinyl; 6-(1,1-dioxidothiazolidin-3-yl)-3-pyridyl; 6-(1,3-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1-oxa-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1,1-dioxidothiomorpholinyl)-3-pyridazinyl; 6-(1-oxa-4,4-dioxido-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1-oxa-4-oxo-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl; 6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-8-yl)-3-pyridyl; 6-(N-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridylsulfonamide; 2-(1,1-dioxidothiomorpholinyl)-5-thiazoyl; 5-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-2-pyrazinyl; 2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-5-thiazoyl; 6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridazinyl; 6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridyl; 6-(4-methoxypiperidinyl)-3-pyridyl; 6-(4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl)-3-pyridazinyl; 6-(4-(4-tetrahydropyranlyoxy)iminopiperidinyl)-3-pyridazinyl; 6-isopropoxy-3-pyridazinyl; 6-(2,4-dioxo-(1H,3H)-quinazolin-3-yl)-3-pyridyl; 6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridazinyl; 6-(4-tetrahydropyranlyoxy)-3-pyridazinyl; 6-morpholinylethoxy-3-pyridazinyl; 6-(4-ethoxypiperidinyl)-3-pyridazinyl; 6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridazinyl; 6-((3aR,6aS)-2-oxo-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-3-pyridyl;

50

5

10

15

20

25

30

35

40

45

50

- 6-(4-(4-tetrapyranyloxyethyl)piperidinyl)-3-pyridazinyl; 6-(3-(R)-tetrahydrofuryloxy)piperidinyl)-3-pyridazinyl; 6-(3-(S)-tetrahydrofuryloxy)piperidinyl)-3-pyridazinyl; 6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl; 6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl; 6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl; 6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl; 6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl; 6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl; 6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl; 6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridazinyl; 6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridyl; 6-(1,5-dioxa-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(4-tertbutyl)piperidinyl)-3-pyridazinyl; 6-(4-N-formyl)piperidinyl-3-pyridazinyl; 6-morpholinyl-3-pyridazinyl; 4-N-1,4-dioxa-8-azaspiro[4.5]decan-8-ylbenzenesulfonamide; 4-(4-dioxa-8-azaspiro[4.5]decan-8-ylcarboxamide)phenyl; 6-(3-methoxy-1,5-dioxa-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(1,5-dioxa-3-hydroxymethyl)-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(S-O-ethyl-2-hydroxymethylpyrrolidinyl)-3-pyridazinyl; 6-(4-acetyl-1-oxa-4,8-diazaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-((2R,3R)-2,3-bis(methoxymethyl)-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-((2S,3S)-2,3-dimethyl-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-(4,4-(cis-1,2-dioxycyclopentane)piperidinyl)-3-pyridazinyl; 6-(4,4-(1S,2S)-dimethoxymethyleneethanedioxy)piperidinyl)-3-pyridazinyl; 6-(4,4-(cis-3,4-dioxy-oxacyclopentane)piperidinyl)-3-pyridazinyl; 6-(4,4-(1,3-dioxy-2-methoxypropylene)piperidinyl)-3-pyridazinyl; 6-(4,4-(1,3-dioxy-2-hydroxymethylpropylene)piperidinyl)-3-pyridazinyl; 6-(4,4-(2-(2,2-spiro-oxacyclopropane-1,3-dioxypropylene)piperidinyl)-3-pyridazinyl; 6-morpholinyl-3-pyridazinyl; 6-(4-morpholinyliminopiperidinyl)-3-pyridyl; 6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridyl; 6-(4-(1,2,4-triazol-1-yl)iminopiperidinyl)-3-pyridyl; 6-(4-ethylpiperidinylcarboxylate)-3-pyridyl; 2-phenylmethyl-3(2H)-pyridazinone-6-yl; 6-(4-(morpholinylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-morpholinylaminocarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N,N-dimethylaminocarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-methyl-N-

55

5

methoxyethylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-hydroxymethylpiperidinyl)-3-pyridyl; 6-(4-hydroxypiperidinyl)-3-pyridyl; 6-(4-N-acetylpirerazinyl)-3-pyridyl; 6-(4-cyanopiperidinyl)-3-pyridyl; 6-(4-N-(4-fluorophenyl)piperazinyl)-3-pyridyl; 4-

10 5 morpholinylbenzenesulfonamide; 4-N-4,4-ethylenedioxypiperidinylbenzenesulfonamide; 4-N-cyclopropylbenzenesulfonamide; 4-piperidinebenzenesulfonamide; 4-(4-cyanopiperidine)benzenesulfonamide; 4-N-cyclopropylmethylbenzenesulfonamide; 4-

15 10 N,N-dimethylaminobzenesulfonamide; 4-N-(S)-2-hydroxymethylpyrrolidinebenzenesulfonamide; 4-(4-

20 15 hydroxypiperidine)benzenesulfonamide; 4-(cis-3,5-dimethylmorpholinyl)benzenesulfonamide; 3-fluoro-4-thiomorpholinylphenyl; 6-(thiomorpholinyl)-3-pyridyl; 6-(4,4-dioxothiomorpholinyl)-3-pyridyl; 4-(4,4-ethylenedioxypiperidinylcarboxamide)phenyl; 4-(N-cyclopropylcarboxamide)phenyl; 4-

25 20 (morpholinylcarboxamide)phenyl; 6-N-cyclopropylamino-3-pyridyl; 4-(4-hydroxypiperidinylcarboxamide)phenyl; 6-(S)-hydroxymethylpyrrolidinyl-3-pyridazinyl; 6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridyl; 6-hexahdropyrimidine)-3-pyridyl; 6-(S)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl; 6-(R)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl; 6-(cis-3,4-dihydroxypyrrolidinyl)-3-pyridyl; 6-[(3aR,6aS)-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-2-one-5-yl]-3-pyridyl; 6-(cis-2,3-dihydroxypyrrolidinyl)-3-pyridazinyl; 6-(S,R-2-

30 25 hydroxymethyl-4-hydroxypyrrolidinyl)-3-pyridyl; 6-(R-2-hydroxymethyl-4-pyrrolidinyl)-3-pyridazinyl; 6-(1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane)-3-pyridyl; 6-(2-imidizolidone-1-yl)-3-pyridyl; 4-(2,4-(1H,3H)-quinazolinedion-3-yl)phenyl; 6-morpholinylcarboxamide-3-pyridazinyl; 6-methoxy-3-pyridazinyl; 6-N,N-diethoxyethylamino-3-pyridazinyl; 6-(4-ethoxymethylpiperidinyl)-3-pyridazinyl; 6-(4-tetrahydropyranylmethyl)piperidinyl)-3-pyridazinyl; 6-(4-

35 30 ethoxyethoxymethylpiperidinyl)-3-pyridazinyl; 6-N-methyl-N-1,3-dioxalanemethylamino)-3-pyridazinyl; 6-(4,4-dioxyethylenecyclohexyloxy)-3-pyridazinyl; 6-dihydroxymethylmethoxy-3-pyridazinyl; 6-(3-pyridyloxy)-3-pyridazinyl; 4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl; 6-(4-N-methyl-N-methoxyethyl)-3-pyridazinyl; 6-(3,4-dimethoxymethoxypyrrolidinyl)-3-pyridazinyl; 6-(trans-3-hydroxy-4-

50

5

methylpyrrolidinyl)-3-pyridazinyl; 6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl; 6-

10

(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl; 6-(cis-3-hydroxy-4-

methoxy-4-methylpyrrolidinyl)-3-pyridyl; 6-(trans-3-cyano-4-hydroxylpyrrolidinyl)-3-pyridyl; 6-(3-

hydroxy-4-tert-butylcarboxamidepyrrolidinyl)-3-pyridyl; 6-(S-2-(4-

5 tetrahydropyranyloxy)methylpyrrolidinyl)-3-pyridazinyl; 6-(2-(4-

tetrahydropyranyloxy)iminopyrrolidinyl)-3-pyridazinyl; 2-morpholinyl-5-thiazoyl; 5-

15

bromo-2-thienyl; 2,5-dimethyl-3-thienyl; 5-chloro-2-thienyl; 2,4-dimethyl-5-thiazoyl; 5-

methyl-2-thienyl; 2-furanyl; 2-(4,4-dioxyethylenepiperidinyl)-5-thiazoyl; 3-thienyl; 3-

methyl-2-thienyl; 2-morpholinyl-4-thiazoyl; 2-morpholinyl-4-trifluoromethyl-5-thiazoyl;

10 5-morpholinyl-2-thienyl; 4-methyl-2-morpholinyl-5-thiazoyl; 2,5-dichloro-3-thienyl; 2,5-

dimethyl-3-furanyl; N-methyl-2-pyrrolyl; 2-N,N-dimethylamino-5-thiazoyl; 2-

morpholinyl-5-thiazoyl; 2-(4,4-dioxythiomorpholinyl)-5-thiazoyl; 1-N-methyl-2-

morpholinyl-5-imidazoyl; 2-morpholinyl-5-oxazolyl; 2-N-methyl-N-methoxyethylamino-

20

5-thiazoyl; 2-N-methyl-N-ethylamino-5-thiazoyl; 2-N-pyrrolidinyl-5-thiazoyl; 2-N-

25 15 methyl-N-propylamino-5-thiazoyl; 2-N,N-diethylamino-5-thiazoyl; 2-(N-

methypiperazinyl)-5-thiazoyl; 2-(N-(2-pyridyl)piperazinyl)-5-thiazoyl; 2-N-methy-N-(2-

pyridylethyl)-5-thiazoyl; 2-(4-oxopiperazinyl)-5-thiazoyl; 2-(4-(N-

morpholinyl)iminopiperazinyl)-5-thiazoyl; 6-N-morpholine-3-pyridinesulfonamide; 2-(4-

oxopiperidinyl)-5-pyrimidyl; 2-(4,4-dioxethylenepiperidinyl)-5-pyrimidyl; 5-(4,4-

30 20 dioxethylenepiperidinyl)-2-pyrazinyl; 5-(4-oxopiperidinyl)-2-pyrazinyl; 6-N-cyclopropyl-

3-pyridinesulfonamide; 6-N-(4,4-dioxethylenepiperidinyl)-3-pyridinesulfonamide; 2-(4-

40 35 (4-tetrahydropyranyloxy)iminopiperidinyl)-5-pyrazinyl; 6-(4-

(phenylmethoxy)iminopiperidinyl)-3-pyridyl; 6-(4-(tert-butyloxy)iminopiperidinyl)-3-

40 45 pyridyl; 6-(4-(cyclohexyloxy)iminopiperidinyl)-3-pyridyl; 6-(4-hydroxyiminopiperidinyl)-

3-pyridyl; 6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl; 6-(4-

methoxyethoxyiminopiperidinyl)-3-pyridyl; 6-(4-(2-thenylmethoxy)iminopiperidinyl)-3-

pyridyl; 6-(4-(4'-(5'H-2-oxyfuranyl)-4-hydroxy)piperidinyl)-3-pyridyl; 6-(4-(1-(4-

4'-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridazinyl; 6-(4-(4'-acetyl-

4'-hydroxypiperidinyl)-3-pyridazinyl; 6-(4-(1-(isopropylcaboxymethoxy)iminoethyl))-4-

45 50 hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(ethylcaboxymethoxy)iminoethyl))-4-

30 hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(ethylcaboxymethoxy)iminoethyl))-4-

55

- 5 hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(methylcaboxymethoxy)iminoethyl))-4-
10 hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(2-tetrahydropyranloxy)iminoethyl))-4-
15 hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(allyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-
20 pyridyl; 6-(4-(1-(ethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-
25 (methoxy)iminocethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(hydroxy)iminoethyl))-4-
30 hydroxypiperidinyl)-3-pyridyl; 6-(4-(2-tetrahydropyranloxy)iminopiperidinyl)-3-pyridyl;
35 6-(4-(isopropylcarboxymethoxy)iminopiperidinyl)-3-pyridyl; 6-(4-hydroxy-4-(1-(4-
40 tetrahydropyranloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(3-
45 butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(2-butyrolactone)-4-
50 hydroxypiperidinyl)-3-pyridazinyl; 6-(4-acetyl-4-hydroxypiperidinyl)-3-pyridyl; 6-(3-
55 hydroxyazetidinyl)-3-pyridyl; 6-(cis-3-hydroxytropanyl)-3-pyridyl; 6-(cis-2,3-
60 dihydroxypiperidinyl)-3-pyridyl; 6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridazinyl;
65 6-(1,2,3,6-tetrahydropyridyl)-3-pyridyl; 6-(4-(N-4'-methoxyphenylcarbamoyl)piperidinyl)-
70 3-pyridazinyl; 6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl; 6-(trans-3,4-bis(N-
75 15 4'-methoxyphenylcarbamoyl)pyrrolidinyl)-3-pyridyl; 6-(trans-3-hydroxytropanyl)-3-
80 pyridyl; 6-(S,S-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl; 6-(R,R-trans-3,4-
85 dihydroxypyrrolidinyl)-3-pyridazinyl; 6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl;
90 6-(8-(1-phenyl-1,3,8-triaza-2-spiro[4,5]deceN-4-one)-3-pyridyl; 6-(8-(1-phenyl-1,3,8-
95 triaza-2-spiro[4,5]deceN-4-one)-3-pyridyl; 6-(4-(2-keto-1-benzimidazolinyl)piperidinyl)-
100 3-pyridazinyl; 6-(4-oxothiomorpholinyl)-3-pyridyl; 6-(4-(2-keto-1-
105 benzimidazolinyl)piperidinyl)-3-pyridyl; 6-(N-methyl-N-(2-pyridylethyl)amino)-3-
110 pyridyl; 6-(N-methyl-N-(4-pyridylethyl)amino)-3-pyridyl; 6-N-(3-pyridylmethyl)amino-3-
115 pyridyl; 6-(2-hydroxymethylpiperidinyl)-3-pyridyl; 6-(4-hydroxy-4-(4-
120 bromophenyl)piperidinyl)-3-pyridyl; 6-(4-N-(2-pyridnyl)piperazinyl)-3-pyridyl; 6-(4-N-
125 (2-hydroxyethoxyethyl)piperazinyl)-3-pyridyl; 6-(4,4-diacetoxyethylthio)piperidinyl)-3-
130 pyridyl; 6-(N-methy-N-(3-pyridylmethyl)amino)-3-pyridyl; 6-(4-pyrrolidinylpiperidinyl)-
135 3-pyridyl; 6-(4-N-cyanomethylpiperazinyl)-3-pyridyl; 6-(3-hydroxypyrroldinyl)-3-pyridyl;
140 6-(4-methylpiperidinyl)-3-pyridyl; 6-(cis-3,5-dimethylmorpholinyl)-3-pyridyl; 6-(4,4-
145 difluoropipridinyl)-3-pyridyl; 6-(4,4-dioxythiomorpholinyl)-3-pyridazinyl; 6-
150 thiazolidinyl-3-pyridyl; 6-(1,1-dioxythiazolidinyl)-3-pyridyl; 6-thiomorpholinyl-3-

5

pyridazinyl; 6-(2,5-dihydropyrrrol-1-yl)-3-pyridyl; 6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridyl; 6-hydroxy-3-pyridazinyl; 6-piperidinyl-3-pyridyl; and 6-(4-tetrahydropyranyloxy)iminopyrrolidinyl-3-pyridyl; 6-morpholinyl-3-pyridyl.

10

5. 5. The method according to claim 3 wherein R³ is selected from the group consisting of:

15

(thiophene-2-yl)methyl; (thiophene-3-yl)methyl; butyl; cycloheptyl; pentyl; thiophene-2-yl; 1-(3-bromophenyl)ethyl; 2-(N-phenylmethoxycarbonyl)aminophenyl; 2-(3-bromophenyl)ethyl; 2-(3-cyanophenyl)methyl; 2-(4-bromophenyl)ethyl; 2-(5-chloro-

20

10 (thiophen-3-yl)phenyl; 2-bromophenyl; 2-furanyl; 2-methylpropyl; 2-phenylethyl; phenylmethyl; 2,3-dimethoxyphenyl; 2,3-methylenedioxyphenyl; 3-(furan-2-yl)phenyl; 3-(thiophen-2-yl)phenyl; 3-(2-pyridyl)phenyl; 3-(3-methoxybenzyl)phenyl; 2-(3-aminopropynyl)phenylmethyl; 3-benzylxyphenyl; 3-bromo-4-fluorophenyl; 3-bromo-5-iodophenyl; 3-bromo-5-methoxyphenyl; 3-bromophenyl; 3-bromophenyl)methyl; 3-

25

15 carboxamidophenyl; 3-chlorophenyl; 3-cyanophenyl; 3-diethylmalonylallylphenyl; 3-dimethylaminophenyl; 3-ethoxyphenyl; 3-fluoro-5-trifluoromethylphenyl; 3-fluorophenyl; 3-hydroxyphenyl; 3-iodophenyl; 3-methoxyethoxyphenyl; 3-methoxyphenyl; 3-methylphenyl; 3-methylsulfonylphenyl; 3-methylthiophenyl; 3-t-butylacrylphenyl; 3-trifluoromethoxyphenyl; 3-trifluoromethylphenyl; 3-vinylpyridinylphenyl; 3,4-

30

20 dichlorophenyl; 3,4-dimethoxyphenyl; 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; 3,5-di(trifluoromethyl)phenyl; 3,5-dibromophenyl; 3,5-dichlorophenyl; 3,5-dimethoxyphenyl; 3,5-dimethylphenyl; 4-(2-propyl)phenyl; 4-(2-propyl)oxyphenyl; 4-benzylxyphenyl; 4-bromophenyl; 4-bromothiophene-2-yl; 4-butoxyphenyl; 4-dimethylaminophenyl; 4-fluoro-3-trifluoromethylphenyl; 4-methoxyphenyl; 4-

35

25 neopentylphenyl; 4-phenoxyphenyl; 5-bromothiophene-2-yl; 5-cyclohexyl; 5-cyclopropyl; 5-hexyl; 5-methyl; 5-phenyl; (2-bromo-5-chlorophenyl)methyl; (2-bromophenyl)methyl; (5-chloro-2-(3-methoxyphenyl)phenyl)methyl; 3-bromophenyl; 2-pyridyl; 2-ethoxyphenyl; 5-ethoxyphenyl; 2,5-dichlorophenyl; 2,5-dimethylphenyl; 3-fluorophenyl; 3-trifluoromethylphenyl; 5-trifluoromethylphenyl; 3,5-diclorophenyl; 4-bromo-2-thienyl; 30 3-bromo-2-thienyl; 3-cyanophenyl; 4-tetrahydropyranyl; 3-indolyl; 5-indolyl; 4-quinolyl;

40

50

55

5

2-bromophenyl; 4-fluorophenyl; 4,4-difluorocyclohexyl; 1,1-dimethyl-3-butenyl; 2,3-dichlorophenyl; isopropyl; and 2-trifluorophenylphenyl.

10

6. The method according to claim 1 wherein the compound is selected from the group consisting of:

15 4-(N-(2,3-dihydroxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-(N-(3-morpholinylpropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

20

10 4-(N-(2-(4-imidazolyl)ethyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-(N-(3-carboxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

25

15 (S)-4-amino-5-(3-bromophenyl)-7-(6-(O-methyl-2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

(S)-4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

35

20 4-amino-5-(4-fluorophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;

40

25 4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazolyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(N-methyl-3-indolyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

50

5

- 4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxycarbonylmethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-dimethylaminophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-dimethylaminophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-(2-propyl)phenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-neopentylphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-butyloxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-(2-propyl)oxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-butoxyphenyl)-7-(4-N-formylpiperazinylphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-benzyl oxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-phenoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-(2-propyl)phenyl)-7-(4-diethylmalonylallylphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-(2-propyl)phenyl)-7-(4-t-butylacylphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3,4-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-t-butylacrylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

50

55

5

- 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-diethylmalonylallylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 5 4-amino-5-(3-vinylpyridinylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-carboxamidophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(3-cyanophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-benzylxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-methoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-bromophenyl)-7-(4-butoxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-(2-pyridyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(3-methylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-chlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(3-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(3-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-phenylpyrido [2,3-d]pyrimidine;
- 40 4-amino-5-(3-bromophenyl)-7-(4-ethylphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-cyanophenyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(3-bromophenyl)-7-(4-hydroxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-iodophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-ethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

50

5

4-amino-5-(3-trifluoromethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3,5-dichlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-hydroxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-piperidinylphenyl)pyrido[2,3-d]pyrimidine;

20

10 4-amino-5-(3-bromophenyl)-7-(4-imidazol-1-yl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-chlorophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-isopropylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-trifluorophenyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(3,4,5-trimethoxyphenyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-(3-methoxybenzyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

35 4-amino-5-(3-methoxyethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3,4-methylenedioxophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(4-ethoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2'-thiophene)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine;

40

25 4-amino-5-(3-dimethylaminophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3,4,5-trimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

30 4-amino-5-(3-bromophenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine;

50

55

5

4-amino-5-(3-bromophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;

10 4-amino-5-(3-bromophenyl)-7-(3,4-methylenedioxyphenyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(thiophen-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3,5-dimethoxyphenyl)-7-(thiophen-2-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-carboxamidophenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(4-(2-methoxy)ethoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-morpholinylphenyl)pyrido[2,3-

20

d]pyrimidine;

4-amino-5-(3-trifluoromethylphenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromo-4-fluorophenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromo-4-fluorophenyl)-7-(2-furanyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-imidazolylphenyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(thiophene-2-yl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(3-pyridyl)phenyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(4-(4-methylpiperidinyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;

35 4-amino-5-(4-bromothiophene-2-yl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

40

25 4-amino-5-(4-bromothiophene-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

4-morpholinyl-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(5-bromothiophene-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

30 50 d]pyrimidine;

55

- 5 4-amino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
10 4-amino-5-(3-bromophenyl)-7-(4-(acetylamino)phenyl)pyrido[2,3-d]pyrimidine;
15 4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
20 4-amino-5-(3,5-dimethoxyphenyl)-7-(5-pyrimidinylphenyl)pyrido[2,3-d]pyrimidine;
25 4-(4-fluorophenyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
30 4-amino-5-(4-bromothiophene-2-yl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;
35 4-amino-5-(4-bromothiophene-2-yl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;
40 4-amino-5-(3-bromo-5-iodophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;
45 4-amino-5-(3,5-di(trifluoromethyl)phenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;
50 4-amino-5-(3,5-di(trifluoromethyl)phenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;
55 4-amino-5-(3,5-dibromophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(4-methylaminophenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;

5 d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(3-amino-4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(3-bromo-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

30

10 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-trifluoroacetyl amino)phenyl)pyrido[2,3-d]pyrimidine;

40

20 4-amino-5-(3-bromophenyl)-7-(4-(dimethylamino)-3-fluorophenyl)pyrido[2,3-d]pyrimidine;

45

15 4-amino-5-(3-bromophenyl)-7-(4-(N-ethyl-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;

50

30 4,4-bis(acetylamino)-5-(3-bromophenyl)-7-(4-(N-methyl-N-acetyl amino)phenyl)pyrido[2,3-d]pyrimidine;

55

20 4-amino-5-(3-bromophenyl)-7-(4-(N-acetyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;

60

35 4-amino-5-(3-bromophenyl)-7-(4-(N-ethylamino)phenyl)pyrido[2,3-d]pyrimidine;

65

40 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

70

45 4-amino-5-(3-bromophenyl)-7-(4-(N-isopropylamino)phenyl)pyrido[2,3-d]pyrimidine;

75

50 4-amino-5-(3-bromophenyl)-7-(4-N-ethyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

80

55 4-amino-5-(3-bromophenyl)-7-(4-N-(3-methoxypropionyl)-N-isopropylamino)phenyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(4-N-(2-(dimethylamino)ethyl)-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(4-(N-(2-(dimethylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-cyanoethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(3-methoxypropionylamino)phenyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-formyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(4-(4-methoxy-2-butyl)phenyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-(N-phthalimidyl)acetyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methyl-N-(trifluoroacetyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-acetyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-cyanophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-cyanophenyl)-7-(4-(N-methyl-N-formylamino)-phenyl)pyrido[2,3-d]pyrimidine;

25 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-formylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

50

5

- 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methoxyethylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2-(dimethylamino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;
- 15 5 4-amino-5-(3-bromophenyl)-7-(2-(N-methoxyethyl-N-methyl amino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2-(N-formyl-N-methyl amino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;
- 20 10 4-amino-5-(3-bromophenyl)-7-(2-(N-methylamino)5-pyrimidinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2-(1-pyrrolidinyl)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;
- 25 15 4-amino-5-(3-bromophenyl)-7-(2-(1-morpholinyl)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(2-oxo-3-oxazolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 30 20 4-amino-5-(3-bromophenyl)-7-(2-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(3-pyridyl)pyrido[2,3-d]pyrimidine;
- 25 35 4-amino-5-(3-(thiophen-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-(furan-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 40 40 4-amino-5-(3-(3-methoxyphenyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 45 45 4-amino-5-(3-chlorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;
- 30 50 4-amino-5-(3-chlorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;

50

- 5 4-amino-5-(3-chlorophenyl)-7-(4-(thiophen-2-yl)phenyl)pyrido[2,3-d]pyrimidine;
10 4-amino-5-(3-chlorophenyl)-7-(4-(5-pyrimidinyl)phenyl)pyrido[2,3-d]pyrimidine;
10 4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;
15 4-amino-5-(4-bromothiophene-2-yl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
5 4-amino-5-(3-bromophenyl)methyl-7-(4-(dimethylamino)phenyl)pyrido[2,3-
d]pyrimidine;
15 4-amino-5-(2-phenylethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;
20 4-amino-5-(2-methylpropyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;
20 4-amino-5-(butyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;
25 4-amino-5-(2-(4-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-
d]pyrimidine;
30 4-amino-5-(butyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
30 4-amino-5-(2-(3-cyanophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-
d]pyrimidine;
35 4-amino-5-(2-(N-phenylmethoxycarbonyl)aminoethyl)-7-(4-
dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
40 4-amino-5-(cycloheptyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
40 4-amino-5-(2-(5-chloro-2-(thiophen-3-yl)phenylmethyl)-7-(4-
dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
45 4-amino-5-(pentyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;
45 4-amino-5-hexyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;
50 4-amino-5-(2-(3-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-
d]pyrimidine;
50 4-amino-5-((2-bromophenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-
d]pyrimidine;
55 4-amino-5-cyclopropyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
55 4-amino-5-cyclohexyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
55 4-amino-5-((2-bromo-5-chlorophenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-
d]pyrimidine;
55 4-amino-5-methyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(2,3-methylenedioxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(2-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3,5-dimethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,4-dichlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

20

10 4-amino-5-(4-fluoro-3-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-piperidinylphenyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-methylthiophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromo-5-methoxyphenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2,3-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

40

25 4-amino-5-(3-methylsulfonylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

45

4-acetylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-formylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

30 30

50

5

4-(methoxyacetyl)amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

10

4-trifluoroacetylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

5

4-pentanoylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

15

4-benzoylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

20

4-(N-BOC-glycyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-(N-phthalimidylglycyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

25

4-(ethoxycarbonyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-(ethylaminocarbonyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

30

4-allylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-(2-(N,N-dimethylamino)ethylamino)-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

35

4-(4-(N,N-dimethylamino)butylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-(N-allyl-N-formylamino)-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

40

4-diacetylamino-5-(p-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-amino-2-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-pyridyl)pyrido[2,3-d]pyrimidine;

50

5

- 4-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-pyrazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2-oxobenzoxazolin-6-yl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(1-methyl-2-oxobenzoxazolin-6-yl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-((5-chloro-2-(3-methoxyphenyl)phenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-((thiophene-2-yl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-((thiophene-3-yl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-((2-bromophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-(N-formyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-(N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-dimethylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-(2-methoxyacetylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-((4-formylamino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-(dimethylamino)acetylamino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-(2-oxo-3-oxazolidinyl)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(2-propyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

50

55

5

4-amino-5-phenylmethyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-(3-aminopropynyl)phenylmethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(1-(3-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(2-furanyl)-7-(4-(N-morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-dimethylamino-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(4-(ureido)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(1-phenylmethyl-3-piperidinyl)-7-(4-

diethylaminophenyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(3-methyl-5-isoxazolyl))-3-

pyridinyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-chloro-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-methoxy-3-pyridinyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-(1,2,4-triazol-4-yl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(2-thiazolyl)-7-(4-pyrrolidinylphenyl)-pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-pyrazolyl-3-pyridinyl)-pyrido[2,3-d]pyrimidine;

40

45

4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-ureido)phenyl)-pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-pyrimidinyl)amino)phenyl)-

pyrido[2,3-d]pyrimidine;

50

4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-methylamino)phenyl)-

pyrido[2,3-d]pyrimidine;

55

5

4-formylamino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-methylsulfonylamino)phenyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methylsulfonylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(1-methyl-5-indolinyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(1-methyl-5-benzimidazolyl)pyrido[2,3-d]pyrimidine;

10 4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3bromophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-pyrazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-(N-(2-methoxyethyl)-N-methylamino)-2-pyrazinyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-bromophenyl)-7-(4-(morpholinylmethyl)-phenyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(5-(N,N-bis(2-methoxyethyl)amino)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

40 4-amino-5-(3-bromophenyl)-7-(4-(imidazolylmethyl)-phenyl)pyrido[2,3-d]pyrimidine;

25 4-amino-5-(3-bromophenyl)-7-(5-(1-morpholinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

45 4-amino-5-(3-bromophenyl)-7-(4-((dimethylamino)methyl)-phenyl)pyrido[2,3-d]pyrimidine;

50

5

4-amino-5-(3-bromophenyl)-7-(5-(4-hydroxy-1-piperidinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(5-(N-formyl-N-methylamino)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(5-(2-propenyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(3-(2-methoxyethyl)-2-oxo-6-benzoxazolyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(4-(1-(N-formylamino)-ethyl)phenyl)pyrido[2,3-d]pyrimidine;

4-(methylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine hydrochloride;

25

4-(2-methoxyethylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine hydrochloride;

15

4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-2-imidazolyl)phenyl)pyrido[2,3-d]pyrimidine trihydrochloride;

30

4-amino-5-(3-bromophenyl)-7-(4-(aminomethyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-bromo-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(4-(dimethylaminoethyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(3-(dimethylamino)propynyl)phenyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(4-(3-amino-3-methylbutynyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-dimethylphosphonatophenyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(4-(3-methoxypropynyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-carboxyphenyl)pyrido[2,3-d]pyrimidine;

50

5

4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)ethyl)-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(2,3-dihydro-3-(dimethylaminoethyl)-2-oxobenzoxazol-6-yl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(2,2,4-trimethyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-cyclohexyl-7-(4-(2-dimethylamino)ethyl)-2H-4H-benzo-3-oxo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-(1-methylethyl)-2-pyridyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(5-piperidin-1-ylpyrid-2-yl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(1-(4-bromophenyl)ethyl)-7-(6-morpholinylpyrid-3-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-((N-formylamino)methyl)phenyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-1-(N-methylamino)ethyl)phenyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(4-(1-(dimethylamino)-1-methylethyl)phenyl)pyrido[2,3-d]pyrimidine;

25 4-amino-5-(3-bromophenyl)-7-(N-acetyl-5-indolinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(6-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-diethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

50

55

5

- 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(4-(N-methyl-N-formyl)amino)-
phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-((2-bromophenyl)methyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-
d]pyrimidine;
- 4-amino-5-(4-tetrahydropyranyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-
d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(1-ethylpropyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclopentyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(2-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3,5-dimethylcyclohexyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-
d]pyrimidine;
- 4-amino-5-((N-(benzyloxycarbonyl)-4-piperidinyl)methyl)-7-(6-morpholinyl-3-
pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-bromo-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(3-cyanophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-dimethylamino-3-
pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridazinyl)pyrido[2,3-
d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(azacycloheptanyl)-3-pyridazinyl)pyrido[2,3-
d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(1-methylethyl))amino)-3-
pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-
d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-(4-acetylpirerazinyl)-3-pyridyl)pyrido[2,3-
d]pyrimidine;

50

55

5

- 4-amino-5-cyclohexyl-7-(6-(4-acetyl-1,4-diazacycloheptanyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-(4-methyl-1,4-diazacycloheptanyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(2-(2-pyridyl)ethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-2-(N-(N',N'-dimethylaminoethyl)-N-methylamino)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-azetidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-(3-(N-methylacetamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-(3-(formamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-(2-methoxymethyl)pyrrolidin-1-yl)pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-(N-methoxyethyl-N-propylamino)pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(N-methyl-N-(2,2-dimethoxyethyl)amino)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-(4-(dimethylamino)piperidinyl)pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-(4-(aminocarbonyl))piperidinyl)pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(N-methyl-N-(3-(diethylamino)propyl)aminopyrid-3-yl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(4-pyridyl)ethylamino)pyrid-3-yl)pyrido[2,3-d]pyrimidine;

50

55

5

4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(3-pyridylmethylamino)pyrid-3-yl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-5-indolyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-2,3-dioxo-5-indolyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(1-morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(4-hydroxy-3-nitrophenyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-(4-formylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromo-4-methoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

50

4-amino-5-(4-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-chlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-chloro-6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

55

4-amino-5-(3-bromophenyl)-7-(6-(N-oxidomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-N-formylamino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-3-pyridyl-N-oxide)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxy)morpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

1-(5-(4-amino-5-(3-bromophenyl)pyrido[2,3-d]pyrimidin-7-yl)-2-pyridyl)-piperidine-4-phosphate, disodium salt;

25

4-amino-5-(3-bromophenyl)-7-(4-methylene)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(4-hydroxy-4-(hydroxymethyl)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

30

15 4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(6-(4-oxo-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-cyclohexyl-7-(6-(4-methylene)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

40

20 4-N-(iminomethyl)amino-5-cyclohexyl-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-allylamino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl) pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(cyclohexyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

50

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazolyl)pyrido[2,3-d]pyrimidine;

5

4-(N-(2,3-dihydroxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

10

4-(N-(3-morpholinylpropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

5

4-(N-(2-(4-imidazolyl)ethyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

15

4-(N-(3-carboxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

20

(S)-4-amino-5-(3-bromophenyl)-7-(6-(O-methyl-2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

25

(S)-4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazolyl)pyrido[2,3-d]pyrimidine;

50

4-amino-5-(N-methyl-3-indolyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

25 4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxycarbonylmethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

45 4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

30 55 4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

5

- 4-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-methoxyiminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-phenylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-methoxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-isobutoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(N-methylpiperezinyl)iminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-tetrahydropyranyloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-morpholinylethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-tetrapyranyloxyethyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(3-(R)-tetrahydrofuranyloxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(3-(S)-tetrahydrofuranyloxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

50

55

- 5 4-amino-5-(3-bromophenyl)-7-(6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 15 5 4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 30 15 4-amino-5-(3-bromophenyl)-7-(6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(3-bromophenyl)-7-(6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 40 4-amino-5-(2-pyridyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 45 25 4-amino-5-(2-bromo-5-ethoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(2,5-dichlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(2,5-dimethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine
- 4-amino-5-(3-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

50

- 5 4-amino-5-(3-trifluoromethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 15 5 4-amino-5-(3,5-dichlorophenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 20 10 4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxa-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 25 15 4-amino-5-(4-bromo-2-thienyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 30 20 4-amino-5-(3-bromophenyl)-7-(6-(4-tertbutyl)piperidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 35 25 4-amino-5-(3-bromophenyl)-7-(6-(4-N-formyl)piperidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 40 30 4-amino-5-(3-bromo-2-thienyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 45 35 4-amino-5-(3-cyanophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 50 40 4-amino-5-(3-bromophenyl)-7-(6-(S-O-ethyl-2-hydroxymethylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 55 45 4-amino-5-(3-bromophenyl)-7-(6-((2S,3S)-2,3-dimethyl-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 60 50 4-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-1,2-dioxycyclopentyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 65 55 4-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-1-oxa-4,8-diazaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 70 60 4-amino-5-(3-bromophenyl)-7-(6-((2R,3R)-2,3-bis(methoxymethyl)-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 75 65 4-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-3,4-dioxy-oxacyclopentyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(6-(3-methoxy-1,5-dioxa-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxa-3-hydroxymethyl-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(6-(1,7,14-trioxa-11-azadispiro[4.2.5.2]pentadecan-11-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(4-tetrahydropyranyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(4-(1,2,4-triazol-1-yl)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(5-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-(4-ethylpiperidinylcarboxylate)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(2-phenylmethyl-3(2H)-pyridazinone-6-yl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(6-(4-(morpholinylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-morpholinylaminocarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

40

25

4-amino-5-(3-bromophenyl)-7-(6-(4-(N,N-dimethylaminocarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methyl-N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-quinolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

50

5

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxymethylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(2-bromophenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

10 10 4-amino-5-(3-bromophenyl)-7-(6-(4-N-acetylpirerazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(4-cyanopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-N-(4-fluorophenyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(4-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

15 15 4-amino-5-(3-bromophenyl)-7-(4-morpholinylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-N-1,4-dioxa-8-azaspiro[4.5]decan-8-ylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

30 20 4-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(4-piperidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(4-cyanopiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylmethylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

25 25 4-amino-5-(3-bromophenyl)-7-(4-N,N-dimethylaminobenzenesulfonamide)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(4-N-(S)-2-hydroxymethylpyrrolidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine;

50

5

4-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(4-(cis-3,5-dimethylmorpholinyl)benzenesulfonamide)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-thiomorpholinylphenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(4-fluorophenyl)-7-(6-(thiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(4-fluorophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

10 4-methoxy-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(4-dioxa-8-azaspiro[4.5]decan-8-ylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(N-cyclopropylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;

30

15 4-amino-5-(3-bromophenyl)-7-(4-(morpholinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-N-cyclopropylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-bromophenyl)-7-(6-(S)-hydroxymethylpyrrolidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

40

25 4-amino-5-(3-bromophenyl)-7-(6-hexahydropyrimidine-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4,4-difluorocyclohexyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-(S)-2-ethoxyethoxypyrrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

50

5

- 4-amino-5-(3-bromophenyl)-7-(6-(R)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 5 4-amino-5-(3-bromophenyl)-7-(6-((3aR,6aS)-2-oxo-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-bromophenyl)-7-(6-(S,R-2-hydroxymethyl-4-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(3-bromophenyl)-7-(6-(R-2-hydroxymethyl-4-pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(3-bromophenyl)-7-(6-(2-imidizolidone-1-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(3-bromophenyl)-7-(6-(2,4-dioxo-(1H,3H)-quinazolin-3-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 40 4-amino-5-(3-bromophenyl)-7-(6-carboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(3-bromophenyl)-7-(6-morpholinylcarboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 50 4-amino-5-(3-bromophenyl)-7-(6-N,N-diethoxyethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 55 4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxymethylpiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranoyloxymethyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

5

- 4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyethoxymethyl(piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-N-methyl-N-1,3-dioxolanemethylamino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 5 4-amino-5-(3-bromophenyl)-7-(6-(1,4-dioxaspiro[4.5]decanyl-8-oxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-bromophenyl)-7-(6-dihydroxymethylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(3-pyridyloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 20 10 4-amino-5-(3-bromophenyl)-7-(6-(4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-N-ethyl-N-methoxyethyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(6-(4-N-methyl-N-methoxyethyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-bromophenyl)-7-(6-(3,4-dimethoxymethoxy-pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 40 4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

50

5

4-amino-5-(3-bromophenyl)-7-(6-(trans-3-cyano-4-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxy-4-tert-butylcarboxamidepyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(6-(S-2-(4-tetrahydropyranyloxy)methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydropyranyloxy)iminopyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;

20

10 4-amino-5-(3-bromophenyl)-7-(5-bromo-2-thienyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-thienyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-chloro-2-thienyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2,4-dimethyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(5-methyl-2-thienyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(2-furanyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(3-thienyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3-methyl-2-thienyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazoyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-trifluoromethyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-thienyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(4-methyl-2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;

25 4-amino-5-(3-bromophenyl)-7-(2,5-dichloro-3-thienyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-furanyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(N-methyl-2-pyrrolyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-N,N-dimethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;

50

30 4-amino-5-(3-bromophenyl)-7-(2-N,N-dimethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;

55

5

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(2-(4,4-dioxythiomorpholinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(2-(1,1-dioxidothiomorpholinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-oxazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-methoxyethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-ethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(2-N-pyrrolidinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-propylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(2-N,N-diethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(2-(N-methylpiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(2-(N-(2-pyridyl)piperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-bromophenyl)-7-(2-N-methy-N-(2-pyridylethyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

45 4-amino-5-(3-bromophenyl)-7-(2-(4-(N-morpholinyl)iminopiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-N-morpholine-3-pyridinesulfonamide)pyrido[2,3-d]pyrimidine;

50

25 4-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperidinyl)-5-pyrimidyl)pyrido[2,3-d]pyrimidine;

45 4-amino-5-(3-bromophenyl)-7-(2-(4,4-dioxethylenepiperidinyl)-5-pyrimidyl)pyrido[2,3-d]pyrimidine;

5

- 4-amino-5-(3-bromophenyl)-7-(5-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-2-pyrazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(5-(4-oxopiperidinyl)-2-pyrazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-N-cyclopropyl-3-pyridinesulfonamide)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(N-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridylsulfonamide)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2-(4-(4-tetrahydropyranlyoxy)iminopiperidinyl)-5-pyrazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-(phenylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-(tert-butyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-(cyclohexyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxyiminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranlyoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-methoxyethoxyiminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-thenylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-(5'H-2-oxyfuranyl)-4-hydroxy)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(4-tetrahydropyranlyoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-acetyl-4'-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

50

5

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(isopropylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(2-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(allyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(hydroxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(isopropylcarboxymethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-bromophenyl)-7-(6-(4-(3-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxy-4-(1-(4-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(3-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxyazetidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

30 4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxyazetidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

50

55

- 5 4-amino-5-(3-bromophenyl)-7-(6-((1R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 15 5 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(3-bromophenyl)-7-(6-(1,2,3,6-tetrahydropyridyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(6-(4-(N-4'methoxyphenylcarbamoyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 30 10 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4- bis(N-4'-methoxyphenylcarbamoyl)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 40 15 4-amino-5-(3-bromophenyl)-7-(6-((1S,5R)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(3-bromophenyl)-7-(6-(S,S-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 50 4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 55 4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 60 4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 65 25 4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-oxo-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 70 4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4,4-dioxido-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 75 4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazolinyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(4-oxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazolinyl)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(2-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(4-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-N-(3-pyridylmethyl)amino-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

15 4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxy-4-(4-bromophenyl)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-N-(2-pyridyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(6-(4-N-(2-hydroxyethoxyethyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4,4-diacetoxyethylthio)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

40

25 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-pyrrolidinylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-(2-(1H-imidazol-4-yl)ethylamino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

30

50

5

4-amino-5-(3-bromophenyl)-7-(6-(4-N-cyanomethylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxypyrroldinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(cis-3,5-dimethylmorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4,4-difluoropipridinyl)-3-pyridyl)pyrido[2,3-

20

10 d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidothiomorpholinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-thiazolidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidothiazolidin-3-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(2,5-dihydropyrrolyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

30

20 4-amino-5-(3-bromophenyl)-7-(6-(1,3-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(6-hydroxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

amino-5-(2,3-dichlorophenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-

pyridyl)pyrido[2,3-d]pyrimidine;

40

25 4-amino-5-isopropyl-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-piperidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydropyranoyloxyimino)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine; and

50

5

4-amino-5-(2-trifluorophenylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

10

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1 in combination with a pharmaceutically acceptable carrier.

15

8. A method of treating ischemia, neurological disorders, nociception, inflammation, immunosuppression, gastrointestinal disfunctions, diabetes and sepsis in a mammal in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound according to Claim 1 or 3.

20

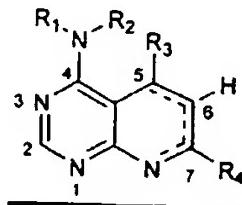
9. A method according to Claim 8 wherein the method consists of treating cerebral ischemia, myocardial ischemia, angina, coronary artery bypass graft surgery, percutaneous transluminal angioplasty, stroke, thrombotic and embolic conditions, epilepsy, anxiety, schizophrenia, pain perception, neuropathic pain, visceral pain, arthritis, sepsis, diabetes and abnormal gastrointestinal motility.

30

10. A compound of formula I

35

20



40

or a pharmaceutically acceptable salt or amide thereof wherein,

45

R¹ and R² are each independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl, heterocycle, heterocycloalkyl, heterocyclo carbonyl, hydroxyalkyl, iminoalkyl, and (NZ₁Z₂)alkyl, or R¹ and R² may join

50

5

together with the nitrogen atom to which they are attached to form a 5-7 membered ring optionally containing 1-2 additional heteroatoms selected from the group consisting of O, N, and S;

10

Z_1 and Z_2 are each independently selected from the group consisting of hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, benzyl, benzyloxycarbonyl, and formyl;

15

R^1 is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, $(NZ_1Z_2)alkyl$, and $-R^A R^B$;

20

R^A is selected from the group consisting aryl and arylalkyl;

25

R^B is selected from aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

30

R^4 is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and $-R^C R^D R^E$;

35

R^C is selected from aryl, arylalkyl, heterocycle, and heterocyclealkyl;

R^D is selected from aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl;

40

R^E is absent or selected from aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;

45

with the proviso that the following compounds are excluded,

4-amino-5-(4-chlorophenyl)-7-(4-nitrophenyl)pyridol[2,3-d]pyrimidine,

4-amino-5-(4-methoxyphenyl)-7-(4-nitrophenyl)pyridol[2,3-d]pyrimidine,

50

4-amino-5-(4-fluorophenyl)-7-(4-fluorophenyl)pyridol[2,3-d]pyrimidine,

4-amino-5-(4-chlorophenyl)-7-(4-fluorophenyl)pyridol[2,3-d]pyrimidine.

30 4-amino-5-phenyl-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine,

55

5

4-amino-5-phenyl-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,
 4-amino-5-(4-methoxyphenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine,
 4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine, and
 4-amino-5,7-diphenylpyrido[2,3-d]pyrimidine.

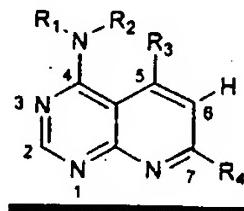
10

5

11. A compound according to claim 10 of formula II

15

20



II,

25

or a pharmaceutically acceptable salt or amide thereof wherein,

30

10 R^1 and R^2 are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl, heterocyclealkyl, hydroxyalkyl, iminoalkyl, and $(NZ_1Z_2)alkyl$, or R^1 and R^2 may join together with the nitrogen atom to which they are attached to form a 6 membered ring

35

15 optionally containing 1 additional heteroatom selected from the group consisting of O, N, and S;

35

Z_1 and Z_2 are each independently selected from the group consisting of hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, benzyl, benzyloxycarbonyl, and formyl;

40

20 R^3 is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heterocyclealkyl, $(NZ_1Z_2)alkyl$, and $-R^A R^B$;

45

R^A is selected from the group consisting of aryl and arylalkyl;

50

R^B is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, and heterocycle;

55

R^4 is selected from the group consisting of alkoxyalkynyl, alkynyl, aryl, heterocycle, and $-R^C R^D R^E$;

R^C is selected from the group consisting of aryl and heterocycle;

50

5

R^D is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleoxy, and heterocyclesulfonyl; and

10

R^E is absent or selected from the group consisting of aryl, arylalkoxy,

5

arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, and heterocycleoxyiminoalkyl.

15

12. A compound according to claim 10 wherein R^4 is selected from the group consisting of:

20

phenyl; thiophene-2-yl; 3-methyl-2-oxobenzoxazolin-6-yl; 2-(dimethylamino)-5-pyrimidinyl; 2-(N-formyl-N-methyl amino)-5-pyrimidinyl; 2-(N-methoxyethyl-N-methyl amino)-5-pyrimidinyl; 2-(N-methylamino)5-pyrimidinyl; 2-(1-morpholinyl)-5-pyrimidinyl; 2-(1-pyrrolidinyl)-5-pyrimidinyl; 2-dimethylamino-5-pyrimidinyl; 2-furanyl;

25

15 2-oxobenzoxazolin-6-yl; 2-pyridyl; 3-(dimethylamino)phenyl; 3-amino-4-methoxyphenyl; 3-bromo-4-(dimethylamino)phenyl; 3-methoxyphenyl; 3-methyl-4-(N-acetyl-N-

30

methylamino)phenyl; 3-methyl-4-(N-formyl-N-methylamino)phenyl; 3-methyl-4-(N-methyl-N-(trifluoroacetyl)amino)phenyl; 3-methyl-4-(N-methylamino)phenyl; 3-methyl-4-pyrrolidinylphenyl; 3-pyridyl; 3,4-dichlorophenyl; 3,4-methylenedioxyphenyl; 3,4,5-

20 trimethoxyphenyl; 4-(acetylamino)phenyl; 4-(dimethylamino)-3-fluorophenyl; 4-(dimethylamino)phenyl; 4-(imidazol-1-yl)phenyl; 4-(methylthio)phenyl; 4-

35

(morpholinyl)phenyl; 4-(N-(2-(dimethylamino)ethyl)amino)phenyl; 4-(N-(2-methoxyethyl)amino)phenyl; 4-(N-acetyl-N-methylamino)phenyl; 4-(N-ethyl-N-

40

formylamino)phenyl; 4-(N-ethylamino)phenyl; 4-(N-formyl-N-(2-

45 methoxyethyl)amino)phenyl; 4-(N-isopropylamino)phenyl; 4-(N-methyl-N-(2-dimethylamino)ethyl)amino)phenyl; 4-(N-methyl-N-(2-

50

phthalimidyl)acetyl)amino)phenyl; 4-(N-methyl-N-(2-cyano)ethylamino)phenyl; 4-(N-

methyl-N-(2-methoxyethyl)amino)phenyl; 4-(N-methyl-N-(3-methoxy)propionylamino)phenyl; 4-(N-methyl-N-acetylamino)phenyl; 4-(N-methyl-N-

formylamino)phenyl; 4-(N-methyl-N-trifluoroacetylamino)phenyl; 4-(N-

55

5

morpholinyl)phenyl; 4-(thiophene-2-yl)phenyl; 4-(ureido)phenyl; 4-(2-(dimethylamino)acetylaminophenyl; 4-(2-methoxyacetylamino)ethyl)amino)phenyl; 4-(2-methoxyethoxyphenyl; 4-(2-oxo-3-oxazolidinyl)phenyl; 4-(4-methoxy-2-butyl)phenyl; 4-(4-methylpiperidinyl)phenyl; 4-(5-pyrimidinyl)phenyl; 4-aminophenyl; 4-bromophenyl; 4-butoxyphenyl; 4-carboxamidophenyl; 4-chlorophenyl; 4-cyanophenyl; 4-diethylaminophenyl; 4-diethylmalonylallylphenyl; 4-dimethylaminophenyl; 4-ethoxyphenyl; 4-ethylphenyl; 4-fluorophenyl; 4-hydroxyphenyl; 4-imidazolylphenyl; 4-iodophenyl; 4-isopropylphenyl; 4-methoxyphenyl; 4-methylaminophenyl; 4-methylsulfonylphenyl; 4-morpholinylphenyl; 4-N-(2-(dimethylamino)ethyl)-N-formylamino)phenyl; 4-N-(3-methoxypropionyl)-N-isopropyl-amino)phenyl; 4-N-ethyl-N-(2-methoxyethyl)amino)phenyl; 4-N-formylpiperazinylphenyl) 4-nitrophenyl; 4-piperidinylphenyl; 4-(3-pyridyl)phenyl; 4-pyrrolidinylphenyl; 4-t-butylacrylphenyl; 5-(dimethylamino)thiophene-2-yl; 5-amino-2-pyridyl; 5-dimethylamino-2-pyrazinyl; 3-dimethylaminopyridazin-6-yl; 5-dimethylamino-2-pyridyl; 5-pyrimidinylphenyl; 6-(N-methyl-N-formylamino)-3-pyridinyl; 6-(N-methyl-N-methoxyethylamino)-3-pyridinyl; 6-(2-oxo-3-oxazolidinyl)-3-pyridinyl; 6-dimethylamino-3-pyridinyl; 6-imidazolyl-3-pyridinyl; 6-morpholinyl-3-pyridinyl; 6-pyrrolidinyl-3-pyridinyl; 6-(2-propyl)-3-pyridinyl; (4-formylamino)phenyl; 6-(4-oxopiperidinyl)-3-pyridazinyl; 6-(4-morpholinyliminopiperidinyl)-3-pyridazinyl; 6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridazinyl; 6-(4-methoxyiminopiperidinyl)-3-pyridazinyl; 6-phenylmethoxy-3-pyridazinyl; 6-(1,1-dioxidothiazolidin-3-yl)-3-pyridyl; 6-(1,3-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1-oxa-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1,1-dioxidothiomorpholinyl)-3-pyridazinyl; 6-(1-oxa-4,4-dioxido-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1-oxa-4-oxo-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl; 6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-8-yl)-3-pyridyl; 6-(N-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridylsulfonamide; 2-(1,1-dioxidothiomorpholinyl)-5-thiazoyl; 5-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-2-pyrazinyl; 2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-5-thiazoyl; 6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridazinyl; 6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridyl; 6-(4-

50

5 methoxypiperidinyl)-3-pyridyl; 6-(4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-
10 isoindolyl)-3-pyridazinyl; 6-(4-(4-tetrahydropyranyl oxy)iminopiperidinyl)-3-pyridazinyl;
15 6-isopropoxy-3-pyridazinyl; 6-(2,4-dioxo-(1H,3H)-quinazolin-3-yl)-3-pyridyl; 6-(4-(N-
20 methylpiperazinyl)iminopiperidinyl)-3-pyridazinyl; 6-(4-tetrahydropyranyl oxy)-3-
25 pyridazinyl; 6-morpholinylethoxy-3-pyridazinyl; 6-(4-ethoxypiperidinyl)-3-pyridazinyl; 6-
30 (1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(4-(2-ethoxyethoxy)piperidinyl)-3-
35 pyridazinyl; 6-((3aR,6aS)-2-oxo-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-3-pyridyl;
40 6-(4-(4-tetrahydropyranyl oxyethyl)piperidinyl)-3-pyridazinyl; 6-(3-(R)-
45 tetrahydrofuranloxy)piperidinyl)-3-pyridazinyl; 6-(3-(S)-
50 tetrahydrofuranloxy)piperidinyl)-3-pyridazinyl; 6-(trans-3-ethoxy-4-
55 hydroxy)pyrrolidinyl)-3-pyridazinyl; 6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-
60 pyridazinyl; 6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl; 6-(trans-3,4-bis-
65 ethoxy)pyrrolidinyl)-3-pyridazinyl; 6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl; 6-(cis-
70 3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl; 6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl;
75 15 6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl; 6-(cis-3-amino-4-
80 hydroxy)pyrrolidinyl)-3-pyridazinyl; 6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridyl; 6-
85 (1,5-dioxa-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(4-tertbutyl)piperidinyl-3-
90 pyridazinyl; 6-(4-N-formyl)piperidinyl-3-pyridazinyl; 6-morpholinyl-3-pyridazinyl; 4-N-
95 1,4-dioxa-8-azaspiro[4.5]decan-8-ylbenzenesulfonamide; 4-(4-dioxa-8-
100 azaspiro[4.5]decan-8-ylcarboxamide)phenyl; 6-(3-methoxy-1,5-dioxa-9-
105 azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(1,5-dioxa-3-hydroxymethyl-9-
110 azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(S-O-ethyl-2-hydroxymethylpyrrolidinyl)-3-
115 pyridazinyl; 6-(4-acetyl-1-oxa-4,8-diazaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-((2R,3R)-
120 2,3-bis(methoxymethyl)-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-((2S,3S)-
125 2,3-dimethyl-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-(4,4-(1S,2S-
130 dimethoxymethylethanedioxy)piperidinyl)-3-pyridazinyl; 6-(4,4-(cis-3,4-dioxy-
135 oxacyclopentane)piperidinyl)-3-pyridazinyl; 6-(4,4-(1,3-dioxy-2-
140 methoxypropylene)piperidinyl)-3-pyridazinyl; 6-(4,4-(1,3-dioxy-2-
145 hydroxymethylpropylene)piperidinyl)-3-pyridazinyl; 6-(4,4-(2-(2,2-spiro-

- 5 oxacyclopropane-1,3-dioxypropylene)piperidinyl)-3-pyridazinyl; 6-morpholinyl-3-
 10 pyridazinyl; 6-(4-morpholinyliminopiperidinyl)-3-pyridyl; 6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridyl; 6-(4-(1,2,4-triazol-1-yl)iminopiperidinyl)-3-pyridyl; 6-(4-ethylpiperidinylcarboxylate)-3-pyridyl; 2-phenylmethyl-3(2H)-
 5 pyridazinone-6-yl; 6-(4-(morpholinylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-morpholinylaminocarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N,N-dimethylaminocarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-hydroxymethylpiperidinyl)-3-
 10 pyridyl; 6-(4-hydroxypiperidinyl)-3-pyridyl; 6-(4-N-acetylpirerazinyl)-3-pyridyl; 6-(4-cyanopiperidinyl)-3-pyridyl; 6-(4-N-(4-fluorophenyl)piperazinyl)-3-pyridyl; 4-morpholinylbenzenesulfonamide; 4-N-4,4-ethylenedioxypiperidinylbenzenesulfonamide; 4-N-cyclopropylbenzenesulfonamide; 4-piperidinebenzenesulfonamide; 4-(4-cyanopiperidine)benzenesulfonamide; 4-N-cyclopropylmethylbenzenesulfonamide; 4-
 15 N,N-dimethylaminobenzenesulfonamide; 4-N-(S)-2-hydroxymethylpyrrolidinebenzenesulfonamide; 4-(4-hydroxypiperidine)benzenesulfonamide; 4-(cis-3,5-dimethylmorpholinyl)benzenesulfonamide; 3-fluoro-4-thiomorpholinylphenyl; 6-(thiomorpholinyl)-3-pyridyl; 6-(4,4-dioxothiomorpholinyl)-3-pyridyl; 4-(4,4-
 20 ethylenedioxypiperidinylcarboxamide)phenyl; 4-(N-cyclopropylcarboxamide)phenyl; 4-(morpholinylcarboxamide)phenyl; 6-N-cyclopropylamino-3-pyridyl; 4-(4-hydroxypiperidinylcarboxamide)phenyl; 6-(S)-hydroxymethylpyrrolidinyl-3-pyridazinyl; 6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridyl; 6-hexahydropyrimidine)-3-pyridyl; 6-(S)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl; 6-(R)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl; 6-(cis-
 25 3,4-dihydroxypyrrolidinyl)-3-pyridyl; 6-[(3aR,6aS)-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-2-one-5-yl]-3-pyridyl; 6-(cis-2,3-dihydroxypyrrolidinyl)-3-pyridazinyl; 6-(S,R-2-hydroxymethyl-4-hydroxypyrrolidinyl)-3-pyridyl; 6-(R-2-hydroxymethyl-4-pyrrolidinyl)-3-pyridazinyl; 6-(1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane)-3-pyridyl; 6-(2-imidizolidone-1-yl)-3-pyridyl; 4-(2,4-(1H,3H)-quinazolinedion-3-yl)phenyl; 6-
 30 morpholinylcarboxamide-3-pyridazinyl; 6-methoxy-3-pyridazinyl; 6-N,N-

50

- 5 diethoxyethylamino-3-pyridazinyl; 6-(4-ethoxymethyl(piperidinyl)-3-pyridazinyl; 6-(4-(4-tetrahydropyranyl(methyl)piperidinyl)-3-pyridazinyl; 6-(4-ethoxyethoxymethyl(piperidinyl)-3-pyridazinyl; 6-N-methyl-N-1,3-dioxalanemethylamino)-3-pyridazinyl; 6-(4,4-dioxyethylenecyclohexyloxy)-3-pyridazinyl;
- 10 5 6-dihydroxymethylmethoxy-3-pyridazinyl; 6-(3-pyridyloxy)-3-pyridazinyl; 4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl; 6-(4-N-methyl-N-methoxyethyl)-3-pyridazinyl; 6-(3,4-dimethoxymethoxypyrrolidinyl)-3-pyridazinyl; 6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl; 6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl; 6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl; 6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl; 6-(trans-3-cyano-4-hydroxypyrrolidinyl)-3-pyridyl; 6-(3-hydroxy-4-tert-butylcarboxamidepyrrolidinyl)-3-pyridyl; 6-(S-2-(4-tetrahydropyranyloxy)methylpyrrolidinyl)-3-pyridazinyl; 6-(2-(4-tetrahydropyranyloxy)iminopyrrolidinyl)-3-pyridazinyl; 2-morpholinyl-5-thiazoyl; 5-bromo-2-thienyl; 2,5-dimethyl-3-thienyl; 5-chloro-2-thienyl; 2,4-dimethyl-5-thiazoyl; 5-methyl-2-thienyl; 2-furanyl; 2-(4,4-dioxyethylenepiperidinyl)-5-thiazoyl; 3-thienyl; 3-methyl-2-thienyl; 2-morpholinyl-4-thiazoyl; 2-morpholinyl-4-trifluoromethyl-5-thiazoyl; 5-morpholinyl-2-thienyl; 4-methyl-2-morpholinyl-5-thiazoyl; 2,5-dichloro-3-thienyl; 2,5-dimethyl-3-furanyl; N-methyl-2-pyrrolyl; 2-N,N-dimethylamino-5-thiazoyl; 2-morpholinyl-5-thiazoyl; 2-(4,4-dioxythiomorpholinyl)-5-thiazoyl; 1-N-methyl-2-morpholinyl-5-imidazoyl; 2-morpholinyl-5-oxazoyl; 2-N-methyl-N-methoxyethylamino-5-thiazoyl; 2-N-methyl-N-ethylamino-5-thiazoyl; 2-N-pyrrolidinyl-5-thiazoyl; 2-N-methyl-N-propylamino-5-thiazoyl; 2-N,N-diethylamino-5-thiazoyl; 2-(N-methylpiperezinyl)-5-thiazoyl; 2-(N-(2-pyridyl)piperazinyl)-5-thiazoyl; 2-N-methyl-N-(2-pyridylethyl)-5-thiazoyl; 2-(4-oxopiperazinyl)-5-thiazoyl; 2-(4-(N-morpholinyl)iminopiperazinyl)-5-thiazoyl; 6-N-morpholine-3-pyridinesulfonamide; 2-(4-oxopiperidinyl)-5-pyrimidyl; 2-(4,4-dioxethylenepiperidinyl)-5-pyrimidyl; 5-(4,4-dioxethylenepiperidinyl)-2-pyrazinyl; 5-(4-oxopiperidinyl)-2-pyrazinyl; 6-N-cyclopropyl-3-pyridinesulfonamide; 6-N-(4,4-dioxethylenepiperidinyl)-3-pyridinesulfonamide; 2-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-5-pyrazinyl; 6-(4-(phenylmethoxy)iminopiperidinyl)-3-pyridyl; 6-(4-(tert-butyloxy)iminopiperidinyl)-3-
- 15 20 25 30 35 40 45 50

5

pyridyl; 6-(4-(cyclohexyloxy)iminopiperidinyl)-3-pyridyl; 6-(4-hydroxyiminopiperidinyl)-3-pyridyl; 6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl; 6-(4-methoxyethoxyiminopiperidinyl)-3-pyridyl; 6-(4-(2-thenylmethoxy)iminopiperidinyl)-3-pyridyl; 6-(4-(4'-(5'H-2-oxyfuranyl)-4-hydroxy)piperidinyl)-3-pyridyl; 6-(4-(1-(4-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridazinyl; 6-(4-(4'-acetyl-4'-hydroxypiperidinyl)-3-pyridazinyl; 6-(4-(1-(isopropylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(ethylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(methylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(2-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(allyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(ethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(hydroxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(2-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl; 6-(4-(isopropylcarboxymethoxy)iminopiperidinyl)-3-pyridyl; 6-(4-hydroxy-4-(1-(4-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(3-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridazinyl; 6-(4-acetyl-4-hydroxypiperidinyl)-3-pyridyl; 6-(3-hydroxyazetidinyl)-3-pyridyl; 6-(cis-3-hydroxytropanyl)-3-pyridyl; 6-(cis-2,3-dihydroxypiperidinyl)-3-pyridyl; 6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridazinyl; 6-(1,2,3,6-tetrahydropyridyl)-3-pyridyl; 6-(4-(N-4'-methoxyphenylcarbamoyl)piperidinyl)-3-pyridazinyl; 6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl; 6-(trans-3,4-bis(N-4'-methoxyphenylcarbamoyl)pyrrolidinyl)-3-pyridyl; 6-(trans-3-hydroxytropanyl)-3-pyridyl; 6-(S,S-trans-3,4-dihydroxypyrrrolidinyl)-3-pyridyl; 6-(R,R-trans-3,4-dihydroxypyrrrolidinyl)-3-pyridyl; 6-(8-(1-phenyl-1,3,8-triaza-2-spiro[4,5]deceN-4-one)-3-pyridyl; 6-(8-(1-phenyl-1,3,8-triaza-2-spiro[4,5]deceN-4-one)-3-pyridyl; 6-(4-(2-keto-1-benzimidazolinyl)piperidinyl)-3-pyridazinyl; 6-(4-oxothiomorpholinyl)-3-pyridyl; 6-(4-(2-keto-1-benzimidazolinyl)piperidinyl)-3-pyridyl; 6-(N-methyl-N-(2-pyridylethyl)amino)-3-pyridyl; 6-(N-methyl-N-(4-pyridylethyl)amino)-3-pyridyl; 6-N-(3-pyridylmethyl)amino-3-pyridyl; 6-(2-hydroxymethylpiperidinyl)-3-pyridyl; 6-(4-hydroxy-4-(4-

50

55

5

10

15

20

25

30

35

40

45

50

bromophenyl)piperidinyl)-3-pyridyl; 6-(4-N-(2-pyridnyl)piperazinyl)-3-pyridyl; 6-(4-N-(2-hydroxyethoxyethyl)piperazinyl)-3-pyridyl; 6-(4,4-diacetoxyethylthio)piperidinyl)-3-pyridyl; 6-(N-methy-N-(3-pyridylmethyl)amino)-3-pyridyl; 6-(4-pyrrolidinyl(piperidinyl)-3-pyridyl; 6-(4-N-cyanomethylpiperazinyl)-3-pyridyl; 6-(3-hydroxypyrrolidinyl)-3-pyridyl; 5 6-(4-methylpiperidinyl)-3-pyridyl; 6-(cis-3,5-dimethylmorpholinyl)-3-pyridyl; 6-(4,4-difluoropipridinyl)-3-pyridyl; 6-(4,4-dioxythiomorpholinyl)-3-pyridazinyl; 6-thiomorpholinyl-3-pyridazinyl; 6-(1,1-dioxythiazolidinyl)-3-pyridyl; 6-thiomorpholinyl-3-pyridyl; 6-(2,5-dihydropyrrolyl)-3-pyridyl; 6-hydroxy-3-pyridazinyl; 6-piperidinyl-3-pyridyl; and 6-(4-tetrahydropyranyloxy)iminopyrrolidinyl-3-pyridyl; 6-morpholinyl-3-pyridyl.

13. A compound according to claim 10 wherein R¹ is selected from the group consisting of:

(thiophene-2-yl)methyl; (thiophene-3-yl)methyl; butyl; cycloheptyl; pentyl; thiophene-2-yl; 1-(3-bromophenyl)ethyl; 2-(N-phenylmethoxycarbonyl)aminophenyl; 2-(3-bromophenyl)ethyl; 2-(3-cyanophenyl)methyl; 2-(4-bromophenyl)ethyl; 2-(5-chloro-2-thiophen-3-yl)phenyl; 2-bromophenyl; 2-furanyl; 2-methylpropyl; 2-phenylethyl; phenylmethyl; 2,3-dimethoxyphenyl; 2,3-methylenedioxophenyl; 3-(furan-2-yl)phenyl; 3-(thiophen-2-yl)phenyl; 3-(2-pyridyl)phenyl; 3-(3-methoxybenzyl)phenyl; 2-(3-aminopropynyl)phenylmethyl; 3-benzyl oxyphenyl; 3-bromo-4-fluorophenyl; 3-bromo-5-iodophenyl; 3-bromo-5-methoxyphenyl; 3-bromophenyl; 3-bromophenyl)methyl; 3-carboxamidophenyl; 3-chlorophenyl; 3-cyanophenyl; 3-diethylmalonylallylphenyl; 3-dimethylaminophenyl; 3-ethoxyphenyl; 3-fluoro-5-trifluoromethylphenyl; 3-fluorophenyl; 3-hydroxyphenyl; 3-iodophenyl; 3-methoxyethoxyphenyl; 3-methoxyphenyl; 3-methylphenyl; 3-methylsulfonylphenyl; 3-methylthiophenyl; 3-t-butylacrylphenyl; 3-trifluoromethoxyphenyl; 3-trifluoromethylphenyl; 3-vinylpyridinylphenyl; 3,4-dichlorophenyl; 3,4-dimethoxyphenyl; 3,4-methylenedioxophenyl; 3,4,5-trimethoxyphenyl; 3,5-di(trifluoromethyl)phenyl; 3,5-dibromophenyl; 3,5-dichlorophenyl; 3,5-dimethoxyphenyl; 3,5-dimethylphenyl; 4-(2-propyl)phenyl; 4-(2-propyl)oxyphenyl; 4-benzyl oxyphenyl; 4-bromophenyl; 4-bromothiophene-2-yl; 4-butoxyphenyl; 4-

5

dimethylaminophenyl; 4-fluoro-3-trifluoromethylphenyl; 4-methoxyphenyl; 4-neopentylphenyl; 4-phenoxyphenyl; 5-bromothiophene-2-yl; 5-cyclohexyl; 5-cyclopropyl; 5-hexyl; 5-methyl; 5-phenyl; (2-bromo-5-chlorophenyl)methyl; (2-bromophenyl)methyl; (5-chloro-2-(3-methoxyphenyl)phenyl)methyl; 3-bromophenyl; 2-pyridyl; 2-ethoxyphenyl; 5-ethoxyphenyl; 2,5-dichlorophenyl; 2,5-dimethylphenyl; 3-fluorophenyl; 3-trifluoromethylphenyl; 5-trifluoromethylphenyl; 3,5-diclorophenyl; 4-bromo-2-thienyl; 3-bromo-2-thienyl; 3-cyanophenyl; 4-tetrahydropyranyl; 3-indolyl; 5-indolyl; 4-quinolyl; 2-bromophenyl; 4-fluorophenyl; 4,4-difluorocyclohexyl; 1,1-dimethyl-3-butenyl; 2,3-dichlorophenyl; isopropyl; and 2-trifluorophenylphenyl.

10

- 10 14. A compound according to claim 10 selected from the group consisting of:
4-(N-(2,3-dihydroxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;
4-(N-(3-morpholinylpropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;
4-(N-(2-(4-imidazolyl)ethyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;
4-(N-(3-carboxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;
20 (S)-4-amino-5-(3-bromophenyl)-7-(6-(O-methyl-2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
4-(S)-4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
40 25 4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(4-fluorophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
45 25 4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;

50

55

5

- 4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazolyl)pyrido[2,3-d]pyrimidine;
- 5 4-amino-5-(N-methyl-3-indolyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxycarbonylmethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 20 10 4-amino-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(4-dimethylaminophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 30 15 4-amino-5-(4-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(4-dimethylaminophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 40 20 4-amino-5-(4-(2-propyl)phenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(4-neopentylphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 50 25 4-amino-5-(4-butyloxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-(2-propyl)oxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-butoxyphenyl)-7-(4-N-formylpiperazinylphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-benzyloxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-phenoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-(2-propyl)phenyl)-7-(4-diethylmalonylallylphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-(2-propyl)phenyl)-7-(4-t-butylacylphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

55

5

- 4-amino-5-(3,4-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-t-butylacrylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-diethylmalonylallylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-vinylpyridinylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-carboxamidophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-cyanophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-benzyoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-methoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-butoxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-(2-pyridyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-methylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-chlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-phenylpyrido [2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-ethylphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

50

55

- 5 4-amino-5-(3-bromophenyl)-7-(4-cyanophenyl)pyrido[2,3-d]pyrimidine;
10 4-amino-5-(3-bromophenyl)-7-(4-hydroxyphenyl)pyrido[2,3-d]pyrimidine;
10 4-amino-5-(3-iodophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
15 4-amino-5-(3-ethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
5 4-amino-5-(3-trifloromethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
15 4-amino-5-(3,5-dichlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
20 4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
20 4-amino-5-(3-hydroxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
25 4-amino-5-(3-bromophenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;
25 4-amino-5-(3-bromophenyl)-7-(4-piperidinylphenyl)pyrido[2,3-d]pyrimidine;
30 4-amino-5-(3-bromophenyl)-7-(4-imidazol-1-yl)phenyl)pyrido[2,3-d]pyrimidine;
35 4-amino-5-(3-bromophenyl)-7-(4-chlorophenyl)pyrido[2,3-d]pyrimidine;
35 4-amino-5-(3-bromophenyl)-7-(4-isopropylphenyl)pyrido[2,3-d]pyrimidine;
40 4-amino-5-(3-bromophenyl)-7-(4-trifluorophenyl)pyrido[2,3-d]pyrimidine;
40 4-amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;
45 4-amino-5-(3-bromophenyl)-7-(3,4,5-trimethoxyphenyl)pyrido[2,3-d]pyrimidine;
50 4-amino-5-(3-(3-methoxybenzyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
55 4-amino-5-(3-methoxyethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
55 4-amino-5-(3,4-methylenedioxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
55 4-amino-5-(3-bromophenyl)-7-(4-ethoxyphenyl)pyrido[2,3-d]pyrimidine;
55 4-amino-5-(3-bromophenyl)-7-(2'-thiophene)pyrido[2,3-d]pyrimidine;
55 4-amino-5-(3-bromophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine;
55 4-amino-5-(3-dimethylaminophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

10 4-amino-5-(3,4,5-trimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3,4-methylenedioxyphenyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(thiophen-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethoxyphenyl)-7-(thiophen-2-yle)pyrido[2,3-d]pyrimidine;

25 4-amino-5-(3-bromophenyl)-7-(4-carboxamidophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(2-methoxy)ethoxyphenyl)pyrido[2,3-d]pyrimidine;

30 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-trifluoromethylphenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;

35 4-amino-5-(3-bromophenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromo-4-fluorophenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromo-4-fluorophenyl)-7-(2-furanyl)pyrido[2,3-d]pyrimidine;

40 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-imidazolylphenyl)pyrido[2,3-d]pyrimidine;

45 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(thiophene-2-yl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(3-pyridyl)phenyl)pyrido[2,3-d]pyrimidine;

40 4-amino-5-(3-bromophenyl)-7-(4-(4-methylpiperidinyl)phenyl)pyrido[2,3-

45 d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-bromothiophene)-7-(4-dimethylaminophenyl)pyrido[2,3-

50 d]pyrimidine;

4-amino-5-(4-bromothiophene-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-

55 d]pyrimidine;

5

4-morpholinyl-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(5-bromothiophene-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(acetylamino)phenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethoxyphenyl)-7-(5-pyrimidinylphenyl)pyrido[2,3-

d]pyrimidine;

20

10 4-(4-fluorophenyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-bromothiophene-2-yl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(4-bromothiophene-2-yl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(5-(dimethylamino)thiophene-2-yl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromo-5-iodophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-di(trifluoromethyl)phenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-

20 d]pyrimidine;

35

4-amino-5-(3,5-di(trifluoromethyl)phenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dibromophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

40

25 4-amino-5-(3,5-dibromophenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-bromothiophene-2-yl)-7-(4-(4-methylpiperidinyl)phenyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3,5-dibromophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

30 4-amino-5-(3-bromophenyl)-7-(3-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

50

55

- 5 4-amino-5-(3-bromophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;
10 4-amino-5-(3-bromophenyl)-7-(3-methoxyphenyl)pyrido[2,3-d]pyrimidine;
15 4-amino-5-(3-bromophenyl)-7-(4-(methylthio)phenyl)pyrido[2,3-d]pyrimidine;
20 4-amino-5-(3-bromophenyl)-7-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidine;
25 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;
30 4-amino-5-(3-bromophenyl)-7-(4-methylaminophenyl)pyrido[2,3-d]pyrimidine;
35 4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;
40 4-amino-5-(3-bromophenyl)-7-(3-amino-4-methoxyphenyl)pyrido[2,3-d]pyrimidine;
45 4-amino-5-(3-bromophenyl)-7-(3-bromo-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;
50 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;
55 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-trifluoroacetylamino)phenyl)pyrido[2,3-d]pyrimidine;
 4-amino-5-(3-bromophenyl)-7-(4-(dimethylamino)-3-fluorophenyl)pyrido[2,3-d]pyrimidine;
 4-amino-5-(3-bromophenyl)-7-(4-(N-ethyl-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;
 4,4-bis(acetylamino)-5-(3-bromophenyl)-7-(4-(N-methyl-N-acetylamino)phenyl)pyrido[2,3-d]pyrimidine;
 4-amino-5-(3-bromophenyl)-7-(4-(N-acetyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;
 4-amino-5-(3-bromophenyl)-7-(4-(N-ethylamino)phenyl)pyrido[2,3-d]pyrimidine;
 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;
 4-amino-5-(3-bromophenyl)-7-(4-(N-isopropylamino)phenyl)pyrido[2,3-d]pyrimidine;

5

- 4-amino-5-(3-bromophenyl)-7-(4-N-ethyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-N-(3-methoxypropionyl)-N-isopropylamino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-N-(2-(dimethylamino)ethyl)-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-(N-(2-(dimethylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-cyano)ethylamino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(3-methoxy)propionylamino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-formyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-(4-methoxy-2-butyl)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-phthalimidyl)acetyl)amino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methyl-N-(trifluoroacetyl)amino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-acetyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-cyanophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-cyanophenyl)-7-(4-(N-methyl-N-formylamino)-phenyl)pyrido[2,3-d]pyrimidine;

50

55

5

- 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-formylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 5 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methoxyethylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-bromophenyl)-7-(2-(dimethylamino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;
- 20 10 4-amino-5-(3-bromophenyl)-7-(2-(N-methoxyethyl-N-methyl amino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(2-(N-formyl-N-methyl amino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;
- 30 15 4-amino-5-(3-bromophenyl)-7-(2-(1-pyrrolidinyl)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(3-bromophenyl)-7-(2-(1-morpholinyl)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;
- 40 20 4-amino-5-(3-bromophenyl)-7-(6-(2-oxo-3-oxazolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 45 25 4-amino-5-(3-bromophenyl)-7-(2-pyridyl)pyrido[2,3-d]pyrimidine;
- 50 4-amino-5-(3-bromophenyl)-7-(3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-(thiophen-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-(furan-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-(3-methoxyphenyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

50

55

5

4-amino-5-(3-chlorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-chlorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-chlorophenyl)-7-(4-(thiophen-2-yl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-chlorophenyl)-7-(4-(5-pyrimidinyl)phenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-bromothiophene-2-yl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)methyl-7-(4-(dimethylamino)phenyl)pyrido[2,3-

10 d]pyrimidine;

20

4-amino-5-(2-phenylethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-methylpropyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(butyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(2-(4-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-

15 d]pyrimidine;

4-amino-5-(butyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(2-(3-cyanophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

d]pyrimidine;

4-amino-5-(2-(N-phenylmethoxycarbonyl)aminoethyl)-7-(4-

20 dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(cycloheptyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-(5-chloro-2-(thiophen-3-yl)phenylmethyl)-7-(4-

dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(pentyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

25 4-amino-5-hexyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-(3-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-((2-bromophenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-

d]pyrimidine;

30 4-amino-5-cyclopropyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

50

- 5 4-amino-5-cyclohexyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-((2-bromo-5-chlorophenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-methyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 20 5 4-amino-5-(2,3-methylenedioxypyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 25 15 4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 30 10 4-amino-5-(2-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 35 20 4-amino-5-(3,5-dimethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 40 25 4-amino-5-(3,4-dichlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 45 30 4-amino-5-(4-fluoro-3-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 50 35 4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;
- 55 40 4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-piperidinylphenyl)pyrido[2,3-d]pyrimidine;
- 50 4-amino-5-(3-methylthiophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 55 4-amino-5-(3-bromo-5-methoxyphenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;
- 60 4-amino-5-(2,3-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 65 4-amino-5-(3-methylsulfonylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

5

4-acetylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

10

4-formylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

5 4-(methoxycetyl)amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

15

4-trifluoroacetylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

10 4-pentanoylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

20

4-benzoylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

25

4-(N-BOC-glycyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

15 4-(N-phthalimidylglycyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

30

4-(ethoxycarbonyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

20 4-(ethylaminocarbonyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

35

4-allylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

40 4-(2-(N,N-dimethylamino)ethylamino)-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

25 4-(4-(N,N-dimethylamino)butylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

45 4-(N-allyl-N-formylamino)-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

30 4-diacetylamino-5-(p-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

50

5

4-amino-5-(3-bromophenyl)-7-(5-amino-2-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-

5 pyrazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-oxobenzoxazolin-6-yl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(1-methyl-2-oxobenzoxazolin-6-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-((5-chloro-2-(3-methoxyphenyl)phenyl)methyl)-7-(4-

20

dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-((thiophene-2-yl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-((thiophene-3-yl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-((2-bromophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(4-(N-formyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-bromophenyl)-7-(4-(N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-dimethylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(2-

40

methoxy)acetyl amino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

25 4-amino-5-(3-bromophenyl)-7-((4-formylamino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(2-

45

(dimethylamino)acetyl amino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(2-oxo-3-oxazolidinyl)phenyl)pyrido[2,3-d]pyrimidine;

50

30 4-amino-5-(3-bromophenyl)-7-(6-(2-propyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

55

- 5 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-phenylmethyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 20 5 4-amino-5-(2-(3-aminopropynyl)phenylmethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 25 15 4-amino-5-(1-(3-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 30 10 4-amino-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;
- 35 20 4-amino-5-(2-furanyl)-7-(4-(N-morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;
- 40 25 4-amino-5-(3-bromophenyl)-7-(2-dimethylamino-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;
- 45 30 4-amino-5-(3-bromophenyl)-7-(4-(ureido)phenyl)pyrido[2,3-d]pyrimidine;
- 50 35 4-amino-5-(1-phenylmethyl-3-piperidinyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 55 40 4-amino-5-(3-bromophenyl)-7-(6-(3-methyl-5-isoxazolyl))-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(3-bromophenyl)-7-(6-chloro-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 50 4-amino-5-(3-bromophenyl)-7-(6-methoxy-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 55 4-amino-5-(3-bromophenyl)-7-(6-(1,2,4-triazol-4-yl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 60 4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;
- 65 40 4-amino-5-(2-thiazolyl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;
- 70 45 4-amino-5-(3-bromophenyl)-7-(6-pyrazolyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 75 50 4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-ureido)phenyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-pyrimidinyl)amino)phenyl)-pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-methylamino)phenyl)-pyrido[2,3-d]pyrimidine;

5

4-formylamino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-methylamino)phenyl)-pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-methylsulfonylamino)phenyl)-pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methylsulfonylamino)-3-

20

pyridinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(1-methyl-5-indolinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(1-methyl-5-benzimidazolyl)pyrido[2,3-

d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridazinyl)pyrido[2,3-

d]pyrimidine;

4-amino-5-(3bromophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-

d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridazinyl)pyrido[2,3-

d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-pyrazinyl)pyrido[2,3-

35

d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-(N-(2-methoxyethyl)-N-methylamino)-2-

pyrazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(morpholinylmethyl)-phenyl)pyrido[2,3-

40

d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-(N,N-bis(2-methoxyethyl)amino)-2-

pyridinyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(4-(imidazolylmethyl)-phenyl)pyrido[2,3-

d]pyrimidine;

50

5

4-amino-5-(3-bromophenyl)-7-(5-(1-morpholinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(4-((dimethylamino)methyl)-phenyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(5-(4-hydroxy-1-piperidinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(5-(N-formyl-N-methylamino)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(5-(2-propenyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3-(2-methoxyethyl)-2-oxo-6-benzoxazolyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(4-(1-(N-formylamino)-ethyl)phenyl)pyrido[2,3-d]pyrimidine;

15 4-(methylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine hydrochloride;

30

4-(2-methoxyethylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine hydrochloride;

4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-2-imidazolyl)phenyl)pyrido[2,3-d]pyrimidine trihydrochloride;

35

4-amino-5-(3-bromophenyl)-7-(4-(aminomethyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-bromo-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(4-(dimethylaminoethyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(3-(dimethylamino)propynyl)phenyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(4-(3-amino-3-methylbutynyl)phenyl)pyrido[2,3-d]pyrimidine;

50

5

- 4-amino-5-(3-bromophenyl)-7-(4-dimethylphosphonatophenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-(3-(methoxypropynyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-carboxyphenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)ethyl)-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2,3-dihydro-3-(dimethylaminoethyl)-2-oxobenzoxazol-6-yl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2,2,4-trimethyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(4-(2-dimethylamino)ethyl)-2H-4H-benzo-3-oxo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(5-(1-methylethyl)-2-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(5-piperidin-1-ylpyrid-2-yl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(1-(4-bromophenyl)ethyl)-7-(6-morpholinylpyrid-3-yl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-((N-formylamino)methyl)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-1-(N-methylamino)ethyl)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-(1-(dimethylamino)-1-methylethyl)phenyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(N-acetyl-5-indolinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-cyclohexyl-7-(6-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine;

50

55

5

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-diethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(4-(N-methyl-N-formyl)amino)-phenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-cyclohexyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-((2-bromophenyl)methyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(4-tetrahydropyranyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(1-ethylpropyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclopentyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-cyclohexyl-7-(2-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethylcyclohexyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-((N-(benzyloxycarbonyl)-4-piperidinyl)methyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-cyclohexyl-7-(6-bromo-3-pyridyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-cyclohexyl-7-(3-cyanophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-dimethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(azacycloheptanyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(1-methylethyl))amino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

50

5

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-cyclohexyl-7-(6-(4-acetyl(piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-cyclohexyl-7-(6-(4-acetyl-1,4-diazacycloheptanyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-cyclohexyl-7-(6-(4-methyl-1,4-diazacycloheptanyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(2-(2-pyridyl)ethyl)amino)-3-

20

pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(6-2-(N-(N',N'-dimethylaminoethyl)-N-methylamino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(6-azetidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-cyclohexyl-7-(6-(3-(N-

methylacetamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(6-(3-(formamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-cyclohexyl-7-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(6-(2-methoxymethyl)pyrrolidin-1-yl)pyridyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-cyclohexyl-7-(6-(N-methoxyethyl-N-propylamino)pyridyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-cyclohexyl-7-(N-methyl-N-(2,2-dimethoxyethyl)amino)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(6-(4-(dimethylamino)piperidinyl)pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-cyclohexyl-7-(6-(4-(aminocarbonyl))piperidinyl)pyridyl)pyrido[2,3-d]pyrimidine;

50

5

4-amino-5-cyclohexyl-7-(N-methyl-N-(3-(diethylamino)propyl)aminopyrid-3-yl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(4-pyridyl)ethylamino)pyrid-3-yl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(3-pyridylmethylamino)pyrid-3-yl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-5-indolyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-2,3-dioxo-5-indolyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(1-morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(4-hydroxy-3-nirophenyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(6-(4-formylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidin;

45

4-amino-5-(3-bromophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromo-4-methoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

50

4-amino-5-(4-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

55

4-amino-5-(3-chlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(5-chloro-6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(N-oxidomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-N-formylamino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-3-pyridyl-N-oxide)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxy)morpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

30

1-(5-(4-amino-5-(3-bromophenyl)pyrido[2,3-d]pyrimidin-7-yl)-2-pyridyl)-piperidine-4-phosphate, disodium salt;

35

4-amino-5-(3-bromophenyl)-7-(4-methylenlpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(4-hydroxy-4-(hydroxymethyl)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

50

4-amino-5-cyclohexyl-7-(6-(4-oxo-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(6-(4-methylenlpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-N-(iminomethyl)amino-5-cyclohexyl-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-allylamino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl) pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxypiperdinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

55

5

4-amino-5-(cyclohexyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazolyl)pyrido[2,3-d]pyrimidine;

5

4-(N-(2,3-dihydroxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

15

4-(N-(3-morpholinylpropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

20

4-(N-(2-(4-imidazolyl)ethyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

25

4-(N-(3-carboxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

(S)-4-amino-5-(3-bromophenyl)-7-(6-(O-methyl-2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

30

(S)-4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(4-fluorophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-

pyridinyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;

50

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazolyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(N-methyl-3-indolyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

55

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

50

5

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxycarbonylmethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

10 4-amino-5-(3-bromophenyl)-7-(6-(4-methoxyiminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-phenylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-methoxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(4-tetrahydropyranloxy)iminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(6-isobutoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-(4-N-methylpiperezinyl)iminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-bromophenyl)-7-(6-(4-tetrahydropyranloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(6-morpholinylethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

40

25 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-tetrapyranyloxyethyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-(3-(R)-tetrahydrofuranyloxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

30 4-amino-5-(3-bromophenyl)-7-(6-(3-(R)-tetrahydrofuranyloxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

50

..

5

4-amino-5-(3-bromophenyl)-7-(6-(3-(S)-tetrahydrofuryloxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

15

4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

35

20

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

40

25

4-amino-5-(2-pyridyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

30

4-amino-5-(2-pyridyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

50

4-amino-5-(2-ethoxyphenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(2-bromo-5-ethoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

55

5

4-amino-5-(2,5-dichlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2,5-dimethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

10

4-amino-5-(3-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-trifluoromethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-

5 d]pyrimidine;

15

4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-

pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dichlorophenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-

pyridyl)pyrido[2,3-d]pyrimidine;

20

10 4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxa-9-azaspiro[5.5]undecan-9-yl)-3-

pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-bromo-2-thienyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-

pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(4-tertbutyl)piperidinyl-3-pyridazinyl)pyrido[2,3-

15 d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-N-formyl)piperidinyl-3-pyridazinyl)pyrido[2,3-

d]pyrimidine;

30

4-amino-5-(3-bromo-2-thienyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-

d]pyrimidine;

20 4-amino-5-(3-cyanophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-Bromophenyl)-7-(6-(S-O-ethyl-2-hydroxymethylpyrrolidinyl)-3-

pyridazinyl)pyrido[2,3,

d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(6-((2S,3S)-2,3-dimethyl-1,4-dioxa-8-azaspiro[4.5]decan-

25 8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-1,2-dioxycyclopentyl)piperidinyl)-3-

pyridazinyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-1-oxa-4,8-diazaspiro[4.5]decan-8-yl)-3-

pyridazinyl)pyrido[2,3-d]pyrimidine;

50

5

- 4-amino-5-(3-bromophenyl)-7-(6-((2R,3R)-2,3-bis(methoxymethyl)-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-3,4-dioxy-oxacyclopentyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 5 4-amino-5-(3-bromophenyl)-7-(6-(3-methoxy-1,5-dioxa-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxa-3-hydroxymethyl)-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-bromophenyl)-7-(6-(1,7,14-trioxa-11-azadispiro[4.2.5.2]pentadecan-11-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(4-tetrahydropyranyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(3-bromophenyl)-7-(6-(4-(1,2,4-triazol-1-yl)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 40 4-amino-5-(3-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(5-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 50 4-amino-5-(3-bromophenyl)-7-(6-(4-ethylpiperidinylcarboxylate)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 55 4-amino-5-(3-bromophenyl)-7-(2-phenylmethyl-3(2H)-pyridazinone-6-yl)pyrido[2,3-d]pyrimidine;
- 60 4-amino-5-(3-bromophenyl)-7-(6-(4-(morpholinylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 65 4-amino-5-(3-bromophenyl)-7-(6-(4-(N-morpholinylaminocarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 70 4-amino-5-(3-bromophenyl)-7-(6-(4-(N,N-dimethylaminocarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

50

5

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methyl-N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(4-quinolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(2-bromophenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(4-N-acetylpirerazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(6-(4-cyanopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(4-morpholinylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

35

20 4-amino-5-(3-bromophenyl)-7-(4-N-1,4-dioxa-8-azaspiro[4.5]decan-8-ylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(4-piperidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine;

25 4-amino-5-(3-bromophenyl)-7-(4-(4-cyanopiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylmethylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(4-N,N-dimethylaminobzenesulfonamide)pyrido[2,3-d]pyrimidine;

30 4-amino-5-(3-bromophenyl)-7-(4-N,N-dimethylaminobzenesulfonamide)pyrido[2,3-d]pyrimidine;

50

- 5 4-amino-5-(3-bromophenyl)-7-(4-N-(S)-2-hydroxymethylpyrrolidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine;
- 15 5 4-amino-5-(3-bromophenyl)-7-(4-(cis-3,5-dimethylmorpholinyl)benzenesulfonamide)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-thiomorpholinylphenyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(4-fluorophenyl)-7-(6-(thiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 30 10 4-amino-5-(4-fluorophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 35 4-methoxy-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 40 4-amino-5-(3-bromophenyl)-7-(4-(4-dioxa-8-azaspiro[4.5]decan-8-ylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;
- 45 15 4-amino-5-(3-bromophenyl)-7-(4-(N-cyclopropylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;
- 50 4-amino-5-(3-bromophenyl)-7-(4-(morpholinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;
- 55 4-amino-5-(3-bromophenyl)-7-(6-N-cyclopropylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 60 20 4-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;
- 65 35 4-amino-5-(3-bromophenyl)-7-(6-(S)-hydroxymethylpyrrolidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 70 40 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 75 45 4-amino-5-(3-bromophenyl)-7-(6-hexahdropyrimidine-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 80 50 4-amino-5-(4,4-difluorocyclohexyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(6-(S)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(R)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-dihydroxypyrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-((3aR,6aS)-2-oxo-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

10 4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypyrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-bromophenyl)-7-(6-(S,R-2-hydroxymethyl-4-hydroxypyrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25 4-amino-5-(3-bromophenyl)-7-(6-(R-2-hydroxymethyl-4-pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

30 15 4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

35 4-amino-5-(3-bromophenyl)-7-(6-(2-imidizolidone-1-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

40 20 4-amino-5-(1,1-dimethyl-3-butenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

25 4-amino-5-(3-bromophenyl)-7-(6-(2,4-dioxo-(1H,3H)-quinazolin-3-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

35 4-amino-5-(3-bromophenyl)-7-(6-carboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

40 4-amino-5-(3-bromophenyl)-7-(6-morpholinylcarboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

45 25 4-amino-5-(3-bromophenyl)-7-(6-methoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-N,N-diethoxyethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

50 45 4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxymethylpiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

55

5

4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranoyloxymethyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyethoxymethylpiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

15

5 4-amino-5-(3-bromophenyl)-7-(6-N-methyl-N-1,3-dioxolanemethylamino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(1,4-dioxaspiro[4.5]decanyl-8-oxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-dihydroxymethylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(3-pyridyloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-(4-N-ethyl-N-methoxyethyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-N-methyl-N-methoxyethyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(6-(3,4-dimethoxymethoxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

40

20 4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

50

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

5

- 4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(trans-3-cyano-4-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 5 4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxy-4-tert-butylcarboxamidepyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-(S-2-(4-tetrahydropyranloxy)methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydropyranloxy)iminopyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 20 10 4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(5-bromo-2-thienyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-thienyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(5-chloro-2-thienyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-bromophenyl)-7-(2,4-dimethyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(5-methyl-2-thienyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(3-bromophenyl)-7-(2-furanyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(3-bromophenyl)-7-(3-thienyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(3-bromophenyl)-7-(3-methyl-2-thienyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazoyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-trifluoromethy-5-thiazoyl)pyrido[2,3-d]pyrimidine;
- 40 25 4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-thienyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(4-methyl-2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(3-bromophenyl)-7-(2,5-dichloro-3-thienyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-furanyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(3-bromophenyl)-7-(N-methyl-2-pyrrolyl)pyrido[2,3-d]pyrimidine;

50

5

4-amino-5-(3-bromophenyl)-7-(2-N,N-dimethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(2-(4,4-dioxythiomorpholinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(2-(1,1-dioxidothiomorpholinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-oxazoyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-methoxyethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-ethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(2-N-pyrrolidinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-propylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(2-N,N-diethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(2-(N-methylpiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(2-(N-(2-pyridyl)piperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(2-N-methy-N-(2-pyridylethyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(2-(4-(N-morpholinyl)iminopiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(6-N-morpholine-3-pyridinesulfonamide)pyrido[2,3-d]pyrimidine;
4-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperidinyl)-5-pyrimidyl)pyrido[2,3-d]pyrimidine;

10

15

20

25

30

35

40

45

50

55

5

4-amino-5-(3-bromophenyl)-7-(2-(4,4-dioxethylenepiperidinyl)-5-pyrimidyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(5-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-2-pyrazinyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(5-(4-oxopiperidinyl)-2-pyrazinyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-N-cyclopropyl-3-pyridinesulfonamide)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(N-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridylsulfonamide)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(2-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-5-pyrazinyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-(4-(phenylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(tert-butyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(6-(4-(cyclohexyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxyiminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-methoxyethoxyiminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-thenylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

45 25 4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-(5'H-2-oxyfuranyl)-4-hydroxy)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(4-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

50

- 5 4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-acetyl-4'-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(isopropylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 15 5 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(2-tetrahydropyranloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 30 10 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(allyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 40 15 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(hydroxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 50 20 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-tetrahydropyranloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 55 4-amino-5-(3-bromophenyl)-7-(6-(4-(isopropylcarboxymethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 60 4-amino-5-(3-bromophenyl)-7-(6-(4-(hydroxy-4-(1-(4-tetrahydropyranloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 65 25 4-amino-5-(3-bromophenyl)-7-(6-(4-(3-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 70 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 75 4-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

- 5 4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxyazetidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-((1R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(6-(1,2,3,6-tetrahydropyridyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(3-bromophenyl)-7-(6-(4-(N-4'-methoxyphenylcarbamoyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4- bis(N-4'-methoxyphenylcarbamoyl)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 40 4-amino-5-(3-bromophenyl)-7-(6-((1S,5R)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(3-bromophenyl)-7-(6-(S,S-trans-3,4-dihydroxypyrrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 50 4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 55 4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 60 4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 65 4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-oxo-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 70 4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4,4-dioxido-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

- 5 4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazolinyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-bromophenyl)-7-(6-(4-oxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazolinyl)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(2-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(4-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 40 4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxy-4-(4-bromophenyl)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 50 4-amino-5-(3-bromophenyl)-7-(6-(4-N-(2-pyridyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 55 4-amino-5-(3-bromophenyl)-7-(6-(4-N-(2-hydroxyethoxyethyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

- 5 4-amino-5-(3-bromophenyl)-7-(6-(2-(1H-imidazol-4-yl)ethylamino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-(4-N-cyanomethylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 15 5 4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxypyrroldinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 20 15 4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 25 10 4-amino-5-(3-bromophenyl)-7-(6-(cis-3,5-dimethylmorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 30 20 4-amino-5-(3-bromophenyl)-7-(6-(4,4-difluoropipridinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 35 15 4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidothiomorpholinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 40 30 4-amino-5-(3-bromophenyl)-7-(6-thiazolidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 45 25 4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidothiazolidin-3-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 50 20 4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 55 25 4-amino-5-(3-bromophenyl)-7-(6-(2,5-dihydropyrroly)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 60 30 4-amino-5-(3-bromophenyl)-7-(6-(1,3-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 65 35 4-amino-5-(3-bromophenyl)-7-(6-hydroxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 70 40 amino-5-(2,3-dichlorophenyl)-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 75 45 4-amino-5-isopropyl-7-(6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 80 50 4-amino-5-(3-bromophenyl)-7-(6-piperidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydropyranloxyimino)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine; and

10

4-amino-5-(2-trifluorophenylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

15

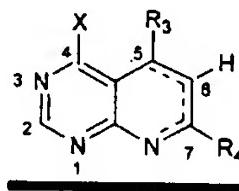
5

15. A pharmaceutical composition comprising a compound according to Claim 10 and a pharmaceutically acceptable carrier.

20

16. A compound of formula III

25
10



wherein X is selected from the group consisting of hydroxy and halogen;

30

R³ is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl,

15

(NZ₁Z₂)alkyl, and -R^AR^B;

35

Z₁ and Z₂ are each independently selected from the group consisting of hydrogen, alkoxy carbonyl, alkyl, alkyl carbonyl, benzyl, benzyloxycarbonyl, and formyl;

40

R^A is selected from the group consisting of aryl and arylalkyl;

45

R^B is selected from aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and

20 heterocyclealkyl;

R⁴ is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and -R^CR^DR^E;

R^C is selected from the group consisting of aryl, arylalkyl, heterocycle, and heterocyclealkyl;

25 R^D is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

50

55

5

10

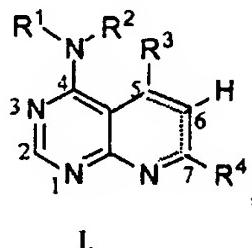
R^E is absent or selected from aryl, arylalkoxy, arylalkoxymino, arylalkyl, aryloxy, heterocycle, heterocylealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained.

15

20

17. A compound according to claim 15 wherein said compound is an intermediate in a process to produce a compound according to claim 10.

18. A process for the preparation of an adenosine kinase inhibiting compound of formula I



30

wherein:

15 R^1 and R^2 are hydrogen;

15 R^3 is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, (NZ_1Z_2) alkyl, and $-R^A R^B$;

20 Z_1 and Z_2 are each independently selected from the group consisting of hydrogen, alkoxy carbonyl, alkyl, alkyl carbonyl, benzyl, benzyloxycarbonyl, and formyl;

40

R^A is selected from the group consisting aryl and arylalkyl;

40 R^B is selected from aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

45

R^4 is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and $-R^C R^D R^E$;

50 R^C is selected from aryl, arylalkyl, heterocycle, and heterocyclealkyl;

5

10

R^D is selected from aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

15

5 R^E is absent or selected from aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

20

a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;

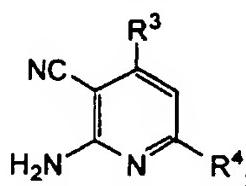
25

the method comprising:

30

(a) reacting a ketone having the formula $R^4\text{-CO-CH}_3$, wherein R^4 is as defined above, with an aldehyde having the formula $R^3\text{-CHO}$, wherein R^3 is as defined above and malononitrile in the presence of an ammonium salt under anhydrous conditions and

15 isolating a first intermediate compound having the structure



35

(b) reacting the first intermediate compound with formamide at reflux for from about 1 to about 8 hours, and isolating the compound of formula I which has a double bond between the 5,6 carbons and a double bond between the 7 carbon and the 8 nitrogen and then,

40

20 (c) optionally reducing the compound from step (b) to form a partially reduced or fully reduced right side of formula I by catalytic hydrogenation.

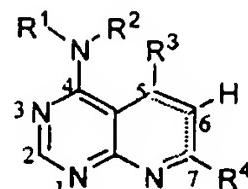
45

50

5

19. A process for the preparation of an adenosine kinase inhibiting compound having the formula

10



15

(I),

5 wherein:

R¹ and R² are hydrogen;

20

R³ is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, (NZ₁Z₂)alkyl, and -R^AR^B;

25

10 Z₁ and Z₂ are each independently selected from the group consisting of hydrogen, alkoxy carbonyl, alkyl, alkyl carbonyl, benzyl, benzyloxycarbonyl, and formyl;

R^A is selected from the group consisting of aryl and arylalkyl;

30

15 R^B is selected from aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

20 R⁴ is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and -R^CR^DR^E;

35

25 R^C is selected from aryl, arylalkyl, heterocycle, and heterocyclealkyl;

40

30 R^D is selected from aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, 20 heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

45

35 R^E is absent or selected from aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl,

50

40 and heterocyclesulfonyl; and

45 a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;

5

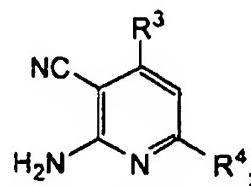
the method comprising

10

(a) reacting a ketone having the formula $R^4C(O)CH_3$, wherein R^4 is as defined above, with an dicyanoalkene compound having the formula $R^3CH=C(CN)_2$, wherein R^3 is as defined above by heating at reflux and isolating a first intermediate compound having the structure

15

5



20

(b) reacting the first intermediate compound with formamide at reflux for from about 1 to about 8 hours, and isolating the compound of formula I which has a double bond between the 5 and 6 carbons and a double bond between the 7 carbon and the 8 nitrogen and

25

10 (c) optionally reducing the compound from step (b) to form a partially reduced or fully reduced right side of formula I by catalytic hydrogenation.

30

35

40

45

50

55

INTERNATIONAL SEARCH REPORT

Int'l. Appl. No.
PCT/US 99/24901

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D471/04 A61K31/519 A61P25/00 A61P9/00 C07D519/00 //(C07D471/04, 239:00, 221:00), (C07D519/00, 471:00, 451:00), (C07D519/00, 471:00, 471:00)		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>SWATI ET AL: "SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME SUBSTITUTED PYRIDO U2,3-DPYRIMIDINES" INDIAN JOURNAL OF PHARMACEUTICAL SCIENCES, XX, XX, vol. 57, no. 6, 1 November 1995 (1995-11-01), pages 229-232, XP002071942 Bombay, India ISSN: 0250-474X table, compounds IIIa-IIIc</p> <p>---</p> <p style="text-align: center;">-/--</p>	7, 10, 11, 15
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		<input checked="" type="checkbox"/> Patent family members are listed in annex.
* Special categories of cited documents : 'A' document defining the general state of the art which is not considered to be of particular relevance 'E' earlier document but published on or after the international filing date 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) 'O' document referring to an oral disclosure, use, exhibition or other means 'P' document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 9 March 2000		Date of mailing of the international search report 22/03/2000
Name and mailing address of the ISA European Patent Office, P.O. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 apo nl, Fax: (+31-70) 340-3016		Authorized officer Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. Appl. No.
PCT/US 99/24901

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>SWATI ET AL: "SYNTHESIS OF SOME PYRIDOU2,3-DPYRIMIDINE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY" HETERO CYCLIC COMMUNICATIONS, IL, FREUND PUBLISHING HOUSE, TEL AVIV, vol. 1, no. 1, 1 January 1994 (1994-01-01), pages 89-94, XP002071943 ISSN: 0793-0283 tables 1 and 2, compounds 6a, 6b ---</p>	7, 10, 11, 15
X	<p>PRAKASH L ET AL: "SYNTHESIS OF SOME NEW 5, 7-DISUBSTITUTED PYRIDO (2,3-D) PYRIMIDINE DERIVATIVES AND THEIR ANTIBACTERIAL ACTIVITY" INDIAN JOURNAL OF HETERO CYCLIC CHEMISTRY, IN, R.S. VERMA, LUCKNOW, vol. 1, no. 1, 1 June 1991 (1991-06-01), pages 21-25, XP002071944 ISSN: 0971-1627 table I, compounds IIa and IIb ---</p>	7, 10, 11, 15
X	<p>A. GUPTA-SHAHLA ET AL.: "Condensation products of 2-amino-3-cyano-4,6-disubstituted pyridine with carbon disulfide, thiourea, urea & formamide and their bacterial activity" IL FAMACO, vol. 47, no. 6, 1992, pages 979-983, XP002132601 Pavia, Italy table I, compounds IIa and IIb ---</p>	7, 10, 11, 15
X	<p>DAVE C G ET AL: "PYRIDOPYRIMIDES: PART III-SYNTHESIS AND ANALGESIC ACTIVITY OF 4-AMINOPYRIDO U2,3-DPYRIMIDINES" INDIAN JOURNAL OF PHARMACEUTICAL SCIENCES, XX, XX, vol. 48, no. 3, 1 May 1986 (1986-05-01), pages 75-77, XP002071945 ISSN: 0250-474X table I, compounds IIb-IIe ---</p>	7, 10-12, 15
X	<p>DAVE C G ET AL: "DIETHYL ETHEXYLMETHYLENEMALONATE IN TRIHETEROCYCLES: A NEW SYNTHESIS OF PYRIDOU3,2-EPYRIMIDOU1,2-CPYRIMIDINES" JOURNAL OF HETERO CYCLIC CHEMISTRY., 1 November 1997 (1997-11-01), XP002071947 HETERO CORPORATION, PROVO., US ISSN: 0022-152X page 1806, compounds 2a-2d ---</p>	10-12
		-/-

INTERNATIONAL SEARCH REPORT

Inte	onal Application No
PCT/US 99/24901	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BAYOUMY B E ET AL: "NEW SYNTHESIS OF PYRIDOPYRIMIDINE AND PYRIOTETRAHYDROQUINOLINE DERIVATIVES" CHEMICAL ABSTRACTS, US, AMERICAN CHEMICAL SOCIETY, COLUMBUS, vol. 116, no. 9, 2 March 1992 (1992-03-02), page 816 XP002071948 ISSN: 0009-2258 -& DATABASE CHEMICAL ABSTRACTS 'Online' Chemical Abstracts Service, Columbus XP002132602 compounds with RNs '138744-54-4' '138744-55-5' '138744-56-6' '138744-57-7' & ZHONGHUA YAOXUE ZAZHI, vol. 43, no. 5, 1991, pages 365-71, ---	10,11,16
X	ROBINS R K ET AL: "STUDIES ON CONDENSED PYRIMIDINE SYSTEMS. XIX. A NEW SYNTHESIS OF PYRIDO2,3-DPYRIMIDINES. THE CONDENSATION OF 1,3-DIKETONES AND 3-KETOALDEHYDES WITH 4-AMINOPYRIMIDINES" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 80, no. 13, 5 July 1958 (1958-07-05), pages 3449-3457, XP002071946 ISSN: 0002-7863 table V, first entry ---	16
X	WO 95 19774 A (WARNER LAMBERT CO) 27 July 1995 (1995-07-27) claims 71,74 ---	7,10,11, 15
X	WO 96 40142 A (PFIZER (US)) 19 December 1996 (1996-12-19) page 22, line 5 - line 16; claim 1 ---	7,10,15
P,X	WO 98 46605 A (ABBOTT LAB) 22 October 1998 (1998-10-22) the whole document -----	1,7,10, 15,16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/24901

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 1 to 6, 8-9 because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1 to 6, 8 and 9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members			International Application No PCT/US 99/24901	
Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
WO 9519774 A	27-07-1995	US 5654307 A AU 686334 B AU 1731495 A AU 686339 B AU 1833495 A BG 100614 A BG 100615 A CA 2177372 A CA 2177392 A CN 1139383 A CN 1139430 A CZ 9601970 A CZ 9601971 A EP 0742717 A EP 0741711 A FI 962855 A FI 962856 A HR 950033 A HR 950034 A HU 74590 A HU 74589 A JP 9508126 T JP 9508127 T MD 960211 A MD 960217 A NO 963093 A NO 963094 A NZ 281404 A PL 315632 A PL 315633 A SK 89496 A SK 89596 A WO 9519970 A US 5679683 A ZA 9500441 A ZA 9500440 A	05-08-1997 05-02-1998 08-08-1995 05-02-1998 08-08-1995 31-03-1997 28-02-1997 27-07-1995 27-07-1995 01-01-1997 01-01-1997 17-09-1997 16-07-1997 20-11-1996 13-11-1996 13-09-1996 25-09-1996 31-10-1997 31-10-1997 28-01-1997 28-01-1997 19-08-1997 19-08-1997 30-04-1998 30-04-1998 24-07-1996 24-07-1996 28-05-1999 25-11-1996 25-11-1996 08-10-1997 06-08-1997 27-07-1997 21-10-1997 10-10-1995 10-10-1995	
WO 9640142 A	19-12-1996	CA 2223081 A HU 9601559 A AP 637 A AU 5479196 A BR 9602695 A CN 1141298 A CZ 9601641 A EP 0831829 A FI 974443 A HR 960269 A JP 10508875 T NO 962386 A NZ 286755 A PL 314641 A SG 45483 A SI 9600184 A SK 72996 A TR 961053 A	19-12-1996 28-02-1997 08-04-1998 19-12-1996 06-10-1996 29-01-1997 11-12-1996 01-04-1998 05-12-1997 31-08-1997 02-09-1998 09-12-1996 25-03-1998 09-12-1996 16-01-1998 30-04-1997 09-04-1997 21-12-1996	
WO 9846605 A	22-10-1998	AU 7108398 A NO 995036 A	11-11-1998 15-10-1999	

Form PCT/ISA/210 (patent family annex) (July 1992)